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INTERCELLULAR SUBSTANCES IN EXPERIMENTAL SCORBUTUS *

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The purpose of this report is to give the results of some simple experiments designed for the purpose of characterizing pathologically (on a histopathologic basis) the scorbutic condition. We have followed the histologic sequences in bone, connective tissue and teeth during the development of the absolute scorbutic condition and the immediate reparative processes following administration of antiscorbutics.

The pathology of human and experimental scorbutus has been extensively studied, and the main facts clearly established in a literature too extensive to be reviewed here. Hess,[1] in his admirable book, gives a good review of the pathology up to 1920. Special mention, however, must be made of the monograph of Aschoff and Koch [2] in 1919, though adequately quoted by Hess, and the monograph of Höjer.[3] The work of Aschoff and Koch is based on human postmortem material, that of Höjer principally on the experimental disease in guinea-pigs. Aschoff and Koch review previous contributions, and their paper deals largely with the changes in bone and cartilage found at costochondral junctions, and at the junctions of diaphyses and epiphyses. From previous work reviewed by them and from their own observations, the important features in the bone pathology may be enumerated as follows: cessation of new bone formation and rarefaction of existing bone of cortex and spongiosa; irregularities, absorption and disappearance of cartilage columns, yielding of the bone under strain and a zone of fragmentation

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1. Hess, A. F.: Scurvy Past and Present, Philadelphia, J. B. Lippincott Company, 1920.

2. Aschoff, L., and Koch, W.: Scorbut, Eine Pathologish-Anatomische Studie, Jena, Gustav Fischer, 1919.

3. Höjer, J. A.: Studies in Scurvy, Acta paediat., supp. **3**:8, 1924.

of bone trabeculae adjacent to the line of junction with cartilage. This is the "trümmerfeld" zone and actual separation by fracture may occur here. Hemorrhages occur. Osteoblasts assume elongated shapes and apparently disappear from regions of bone formation.

The marrow spaces of the shaft adjacent to the cartilage or trümmerfeld zone if that is present becomes filled with a loose textured connective tissue structure described as edematous or gelatinous. This is the "gerüstmark." In repair islands of bone formation make their appearance in subperiosteal regions and in the gerüstmark. Aschoff and Koch explain the condition as one of failure of osteoblasts to form osteoid tissue because of lack of essential materials. By inference they postulate a failure of cement substance in blood vessels, thus accounting for the hemorrhages.

Höjer's description of the bone changes does not materially differ from the foregoing, but he objects to Aschoff and Koch's hypothesis, and ascribes the deficient bone formation to . . . "a degeneration, or rather a receding of the bone forming cells, these being changed so as to form a qualitatively more and more degenerate as well as quantitatively more and more reduced bone, till their activity eventually leaves altogether." He therefore attributes the pathologic condition to defective function of cells, and excludes the factor of materials available by the osteoblasts. We believe that Höjer's interpretation was based on observations on animals in incomplete or partial scorbutus. Höjer's studies of changes in the incisor teeth were extensive and are beautifully illustrated. The incisors of rodents have "open roots" and continue to grow through the life time of the animals. Höjer's summary of the changes in teeth includes changes in morphology and arrangement of the odontoblasts, amorphous calcification of the predentin, new formation of bone instead of dentin by the odontoblasts, atrophy and resorption of pulp tissue, newly formed bone and the old dentin. In the healing of scorbutus he describes the "reorganization of the pulpa bone into irregular dentin, osteodentin with bone canals and dentinal canals."

We do not question the accuracy of Höjer's description. His findings are different in important respects from ours, as we found in the state of complete scorbutus no formation of "osteodentin" or pulp bone. We believe that his diets were not completely deficient, because we obtained tooth conditions answering to his descriptions only in guinea-pigs fed alternately on deficient and normal foods.

Höjer also demonstrates satisfactorily that in tuberculosis in scorbutic guinea-pigs there is much less collagen deposited by fibroblasts in the periphery of the tuberculous lesions. He also maintains without satisfactory presentation of evidence that there is in general an atrophy of collagen in connective tissue of various organs and in blood vessels, thus accounting for hemorrhages.

Our brief treatment of these two monographs is wholly inadequate for the credit they deserve for accuracy of description, illustrations and significance of conclusions. We have endeavored only to indicate how each has defined the problem of the pathogenesis of the scorbutic condition. Our own work was formulated and begun before Höjer's monograph appeared. While we have studied every tissue and organ from our animals, the present account concerns only the following observations made on guinea-pigs in the state of absolute scorbutus and during early repair following the administration of antiscorbutics: (1) sequences in the incisor teeth, (2) sequences in bones of growing guinea-pigs, (3) sequences in the repair of soft tissues and (4) sequences in the repair of bone injury.

Our results corroborate completely and extend the deductions of Aschoff and Koch, so that we characterize the scorbutic state as one due to the inability of cells of supporting tissues to produce intracellular substances and to maintain existing intracellular substances. In our descriptions of experiments we have purposely omitted histologic minutiae, and the account of structures not relevant to our thesis.

THE DIET

The diet employed by us consisted of soy beans, 50 parts; rolled oats, 29 parts; dried milk powder (Klim), 10 parts; brewers' yeast, 4 parts; butter, 5 parts; calcium carbonate, 1 part, and sodium chlorid, 1 part.

The soy beans were heated in the autoclave at 15 pounds for forty-five minutes as suggested by Mendel. The yeast (trade name Majestic) was obtained from the Liberty Yeast Company of Cambridge, Mass. The inorganic salts compensate the mineral deficiency of the cereal and legume. The ingredients were ground and the food thoroughly mixed, moistened with distilled water, rolled into thin sheets and dried in the incubator. Filter paper was given for roughage. This diet is deficient only in antiscorbutic substance. Eight cubic centimeters of orange juice daily was sufficient to afford complete protection against scorbutic symptoms. The animals ate on the average from 10 to 17 Gm. of the cracker daily. On this diet we have reared guinea-pigs after weaning to 3 or 4 years of age. Some of the animals attained a weight of more than 1,500 Gm. Reproduction also occurred normally on this diet.

The animals were kept in individual cages in a well lighted room with a nearly constant temperature. The cages and feeding dishes were kept scrupulously clean and the food given fresh twice daily.

The initial weight of most of the guinea-pigs used in our work was between 200 and 250 Gm.; a few weighed between 250 and 300 Gm.

SEQUENCES IN THE INCISOR TEETH IN SCORBUTUS AND IN REPAIR

These studies were made on sections through the skull at three levels, each including the upper incisor teeth. The lower incisors were studied in sections at the level of the first molars. The material was fixed in Zenker's fixative, decalcified in 5 per cent nitric acid, embedded in celloidin and stained with hematoxylin and eosin. Sections for comparison were occasionally stained with Van Gieson's stain and Mallory's connective tissue stain.

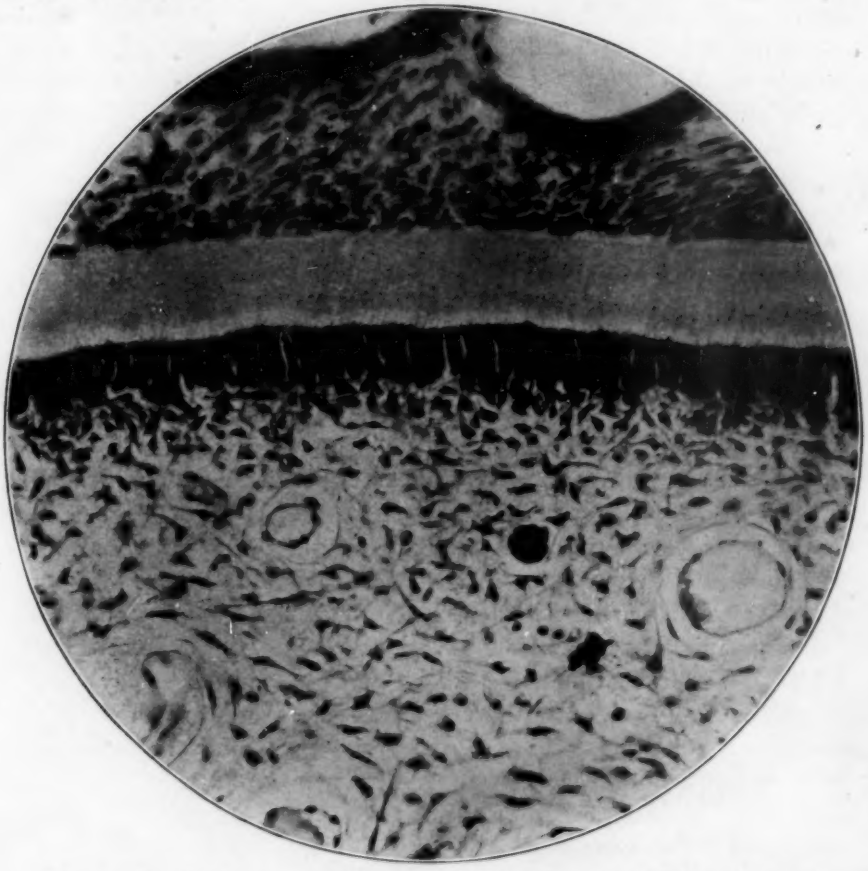

Fig. 1.—Detail of cross section of upper incisor of normal guinea-pig showing layer of odontoblasts, dentin and pulp. × 367.

In from seven to twelve days important changes were found in the odontoblast layer. As Höjer has pointed out, these changes occur first at the apical end of the tooth. The normal odontoblast layer shown in figure 1 consists of cells in orderly array and closely applied to a homogeneously staining dentin. The earliest evidences of scorbutus were separation of this layer from the dentin by a narrow margin,

occasional irregular calcium deposits in the odontogenic zone (predentin) and irregularities in the odontoblast layer. The individual cells became smaller, and they stained more densely. The blood vessels in the adjacent pulp and capillaries in contact with and penetrating the odontoblast layer were more apparent through engorgement. In the odontogenic zone (predentin) there were occasional deposits of basic staining granular material interpreted as due to calcium salts, while between the

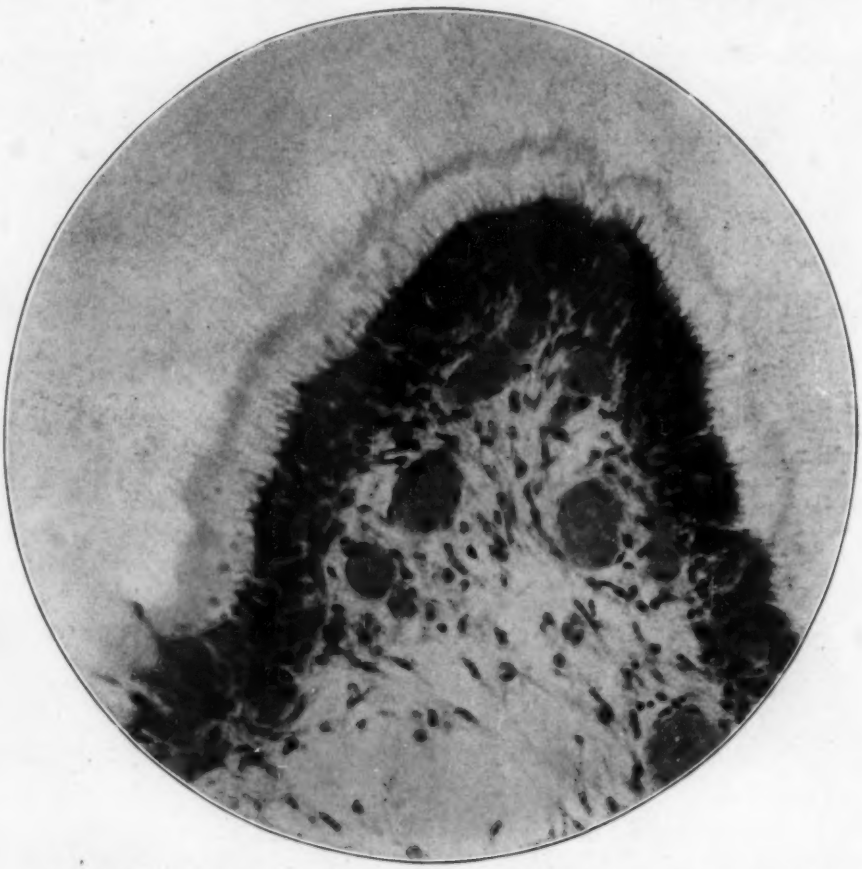

Fig. 2.—Incisor tooth showing early changes in dentin formation and beginning separation of layer of odontoblasts. Seven days on scorbutic diet. × 367.

processes of the odontoblasts evidences of continued dentin formation could be inferred because of the presence of globules of hyaline material which we interpreted as the matrix of spherites (fig. 2).

After a longer period, from twelve to fourteen days, we found the complete separation of odontoblasts from dentin. There was rupture of the processes of odontoblasts, and the spaces separating odontoblasts

and dentin contained no stainable material. Such spaces appeared first as vacuoles, and the conclusion that the accumulation of liquid material caused the separation was unavoidable (fig. 3).

The odontoblasts exhibited changes, the chief of which were diminution in size and increased density of staining. There were also changes in the pulp, edema in places and the deposit of finely granular material between the connective tissue cells possibly representing early deposit of calcium salts.

Fig. 3.—Incisor tooth showing separation of layer of odontoblasts and formation of vacuoles between dentin and odontoblast layer. The cleavage between dentin and zone of lime salt deposit is an artefact. The odontoblasts are diminished in size. Twelve days on scorbutic diet. × 367.

Finally, we had in absolute scorbutus the picture of a shrunken pulp completely freed from the dentin and apparently floating in a liquid material (fig. 4).

Contrary to Höjer, we found no formation of bone in the teeth in complete scurvy. The new formation of intracellular material matrix of bone and of dentin had ceased.

The administration of orange juice resulted in the prompt appearance of new dentin. In twenty-four hours, the administration of only 2 cc. of orange juice to a guinea-pig kept for twelve days on the scorbutic diet resulted in the formation of a zone of dentin on the separated odontoblasts. Eight cubic centimeters of orange juice daily for three days resulted in the complete filling of the space between dentin and odontoblasts in scorbutus of long standing (figs. 5 and 6). The newly formed dentin may be thicker than the original dentin and follows

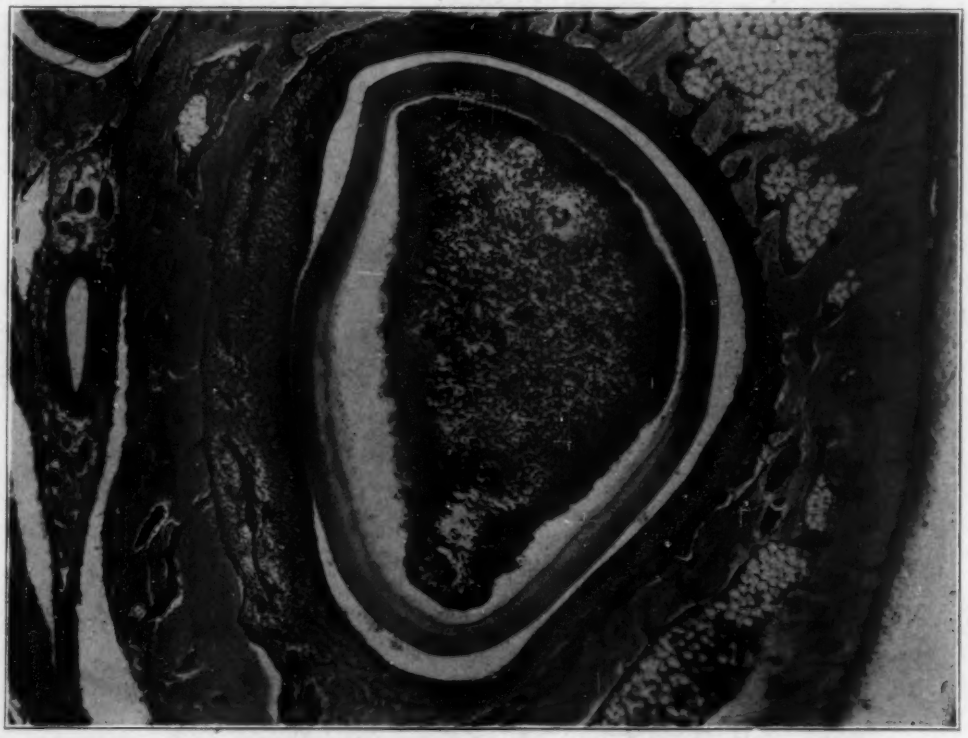

Fig. 4.—Incisor tooth. Fourteen days on scorbutic diet. There is almost complete separation of the pulp from the dentin with rupture of the processes of odontoblasts.

the irregular contours of the odontoblast layer resulting from the scorbutic state.

Examination at twenty-four and forty-eight hour intervals after the addition of orange juice to the diet showed that the filling of the space by dentin proceeded from the surface of the osteoblasts outward. The rapidity of its formation, however, and its appearance before any discernible restoration of the odontoblasts to normal size and staining reac-

tions indicate that the process is one of setting or jelling of a liquid material. On this basis we may assume that the liquid separating odontoblasts and dentin in absolute scorbutus is a defective product of odontoblasts secreted in excess of the normal rate. This explanation must be accepted to account for the large volume of dentin as compared with the original dentin produced in so short a period. The missing factor or agent which the antiscorbutic enables the odontoblasts to supply is evidently one effecting the jelling or setting.

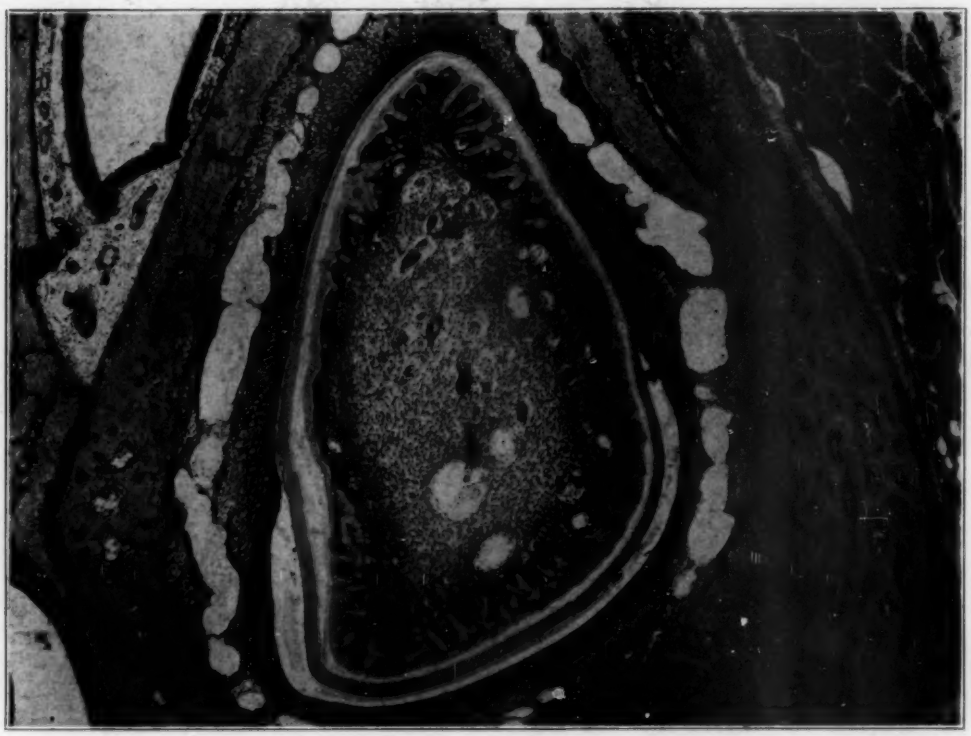

Fig. 5.—Incisor tooth. Fourteen days on scorbutic diet followed by three days with addition of orange juice. The guinea-pig was killed seventy-two hours after the first administration of orange juice. Note the newly formed dentin.

SEQUENCES IN BONES OF GROWING GUINEA-PIGS

The ribs of guinea-pigs gave us the best material for the study of scorbutic sequences because they became completely decalcified in twenty-four hours in Zenker's fixative, and because paraffin embedding and thin sectioning was possible. Accordingly, our most careful studies were made on ribs. A modified Giemsa stain was employed for routine, as we found it gave results superior to hematoxylin-eosin in the study of

cells, calcium salt deposits and matrices of cartilage and bone. Van Gieson's stain, Mallory's phosphotungstic acid hematoxylin and connective tissue stain were also used on selected material.

In addition to the ribs, we made studies from forty-five guinea-pigs on the bones of the skull, the scapula, the humerus including the shoulder joint, the femur including the hip joint and the femur and tibia including the knee joint. All this material was decalcified in 5 per cent nitric acid embedded in celloidin and stained with hematoxylin-eosin.

Fig. 6.—Incisor tooth. Nineteen days on scorbutic diet followed by seven days with addition of orange juice. The guinea-pig was killed seven days after the first administration of orange juice. The new dentin is irregularly traversed by processes of odontoblasts not continued into the old dentin. × 300.

The observations we record as of importance, although made on study of the ribs, were confirmed by the study of the other material. The sequences in costochondral junctions in growing guinea-pigs are qualitatively the same as those in the epiphysial line region of other bones.

We make no attempt to improve on the objective descriptions of the bone histology in scorbutus. We limit ourselves to observations on the

periosteum and growth of bone in relation to cartilage, in complete scorbutus and early reparative response to antiscorbutic treatment.

The Periosteum.—The rarefaction (osteoporosis) of cortical bone is an established observation in experimental as well as in human scorbutus. After from seven to nine days of the scorbutic diet, an increase in spindle-shaped basic staining cells was found in the

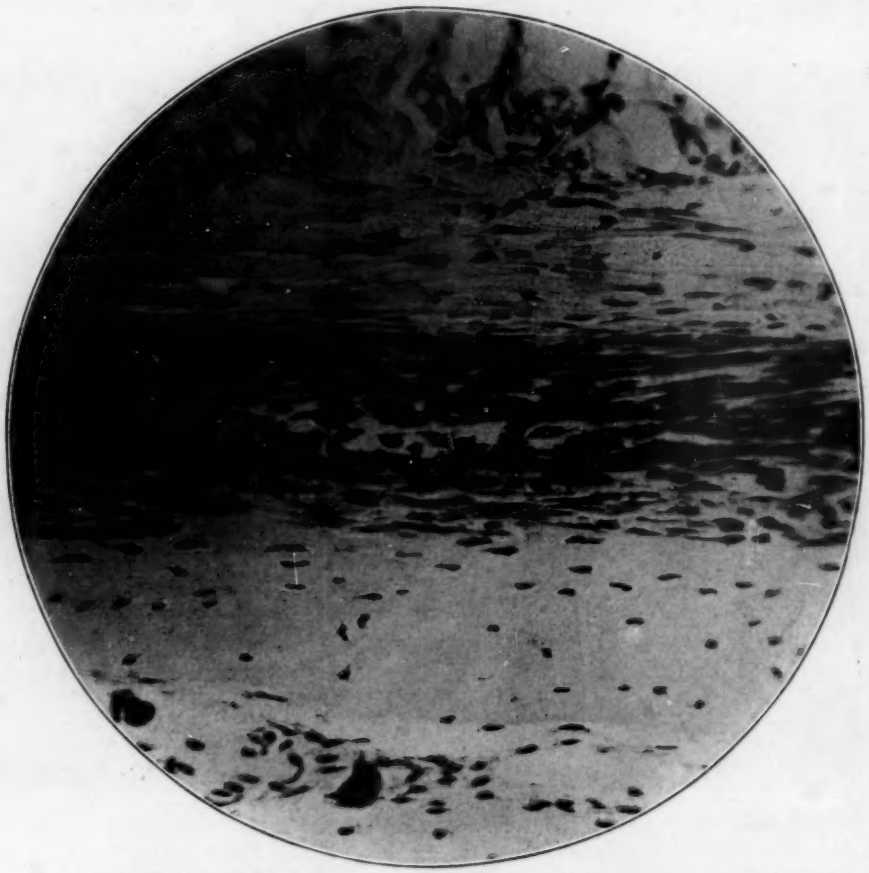

Fig. 7.—Periosteum. Rib of guinea-pig twelve days on scorbutic diet followed by a single dose of 2 cc. of orange juice and killed twenty-four hours later. There has been an increase of spindle shaped osteoblasts, some of which have formed bone matrix following the administration of orange juice. ×266.

osteogenic zone of the periosteum. Multiplication of these cells continued by mitotic division up to the twelfth to the nineteenth day. These accumulations of cells were not uniformly distributed on the individual bone. They have been observed in ribs, jaws, scapula, pelvis, long bones and skull. One determining factor we believe to be

mechanical stress, because the accumulations were greatest where there were muscular attachments. These cells were without intercellular substance. The addition of orange juice to the diet in twenty-four hours produced a change in the morphology of these cells and the deposition of a homogeneous matrix between them (fig. 7). Continuation of the orange juice for from three to six days was sufficient to yield

Fig. 8.—Rib showing cortex and periosteum with recent bone formation. From a guinea-pig kept for ten days on the scorbutic diet followed by six days with the addition of orange juice; killed on sixth day after the first administration of orange juice. × 367.

a fairly extensive layer of osteoid tissue (fig. 8). In as short a period as six days trabeculated new bone was present.

Repeated observations of the foregoing sequences in all the situations mentioned compel the conclusions that for a period after the state of complete scorbutus is established the osteoblasts on the surfaces of

growing bone continue to multiply in the form of spindle-shaped cells, unable to produce intercellular material, and that the administration of antiscorbutics is followed by a prompt formation of bone matrix and the resumption of osteoblast morphology. We shall not endeavor to describe the end-result of continued scorbutus in the periosteum, because of the complicated picture resulting from hemorrhages, and because it is not pertinent to the present thesis.

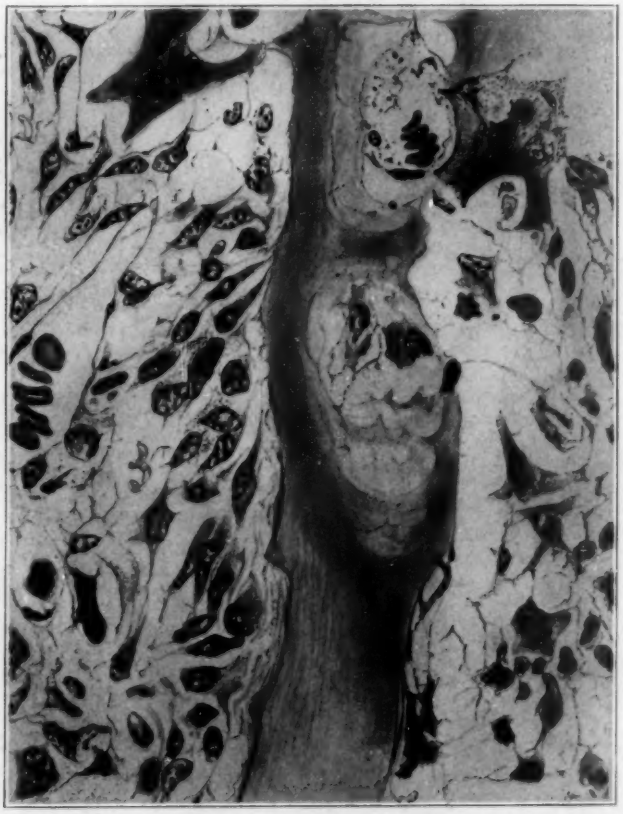

Fig. 9.—Costochondral junction of a guinea-pig after twelve days on the scorbutic diet. The drawing shows an increase in number and a change in the morphology of the osteoblasts adjacent to a bone column in continuity with the cartilage. Resorption of the bone is also apparent. × 675.

Costochondral Junctions.—After from seven to nine days on the scorbutic diet, there was an increase in the number of osteoblasts applied to the ossifying cartilage columns (fig. 9). As in the case of the periosteum, the osteoblasts became spindle-shaped, were intensely basic in staining reaction and were frequently in mitotic division. The proof

that these spindle-shaped cells were osteoblasts was furnished by the fact that they produced bone matrix after the giving of orange juice to a companion scorbutic guinea-pig.

In a later stage, from twelve to sixteen days, on the scorbutic diet, these cells of osteoblastic origin were found at a considerable distance

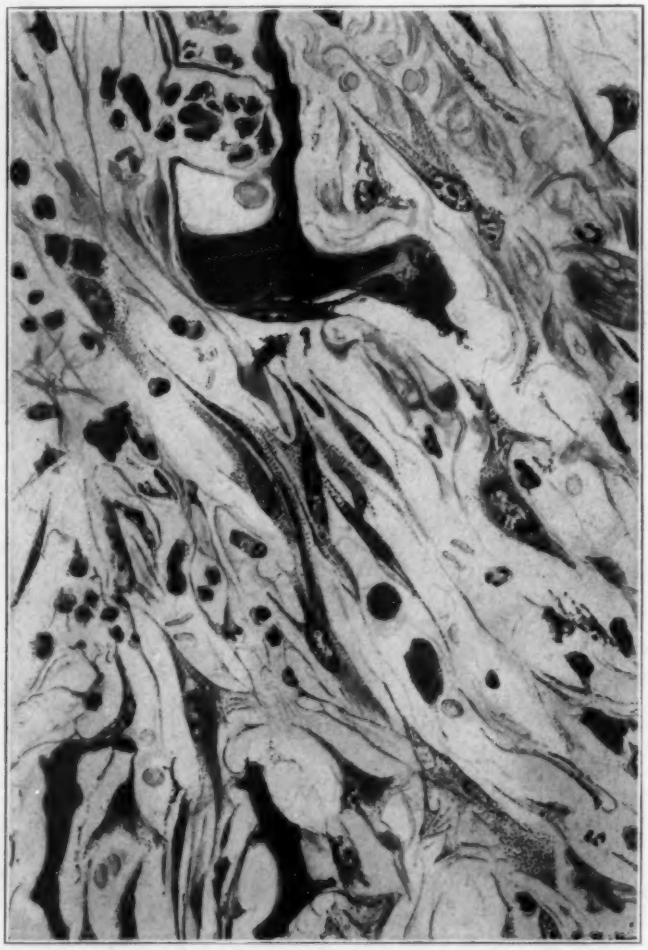

Fig. 10.—Costochondral junction of a guinea-pig after nineteen days on the scorbutic diet. The deeply stained structures are remnants of cartilage columns. The marrow has now assumed the appearance of the gerüstmark of German authors. It is impossible to distinguish between osteoblasts and fibroblasts. × 540.

from the cartilage columns. Mitotic figures continued to be numerous. The succession of histologic appearances between the seventh and twelfth to sixteenth day of diet indicated that the osteoblasts migrated from

their original position and assumed the shapes of fibroblasts; meanwhile mitotic division continued (fig. 10). During this period there was resorption of the bone deposited on calcified cartilage columns. The source of the cells composing the gerüstmark (framework marrow) is thus seen to be from osteoblasts. The appearance of the gerüstmark is that of a loosely textured connective tissue frequently described as edema-

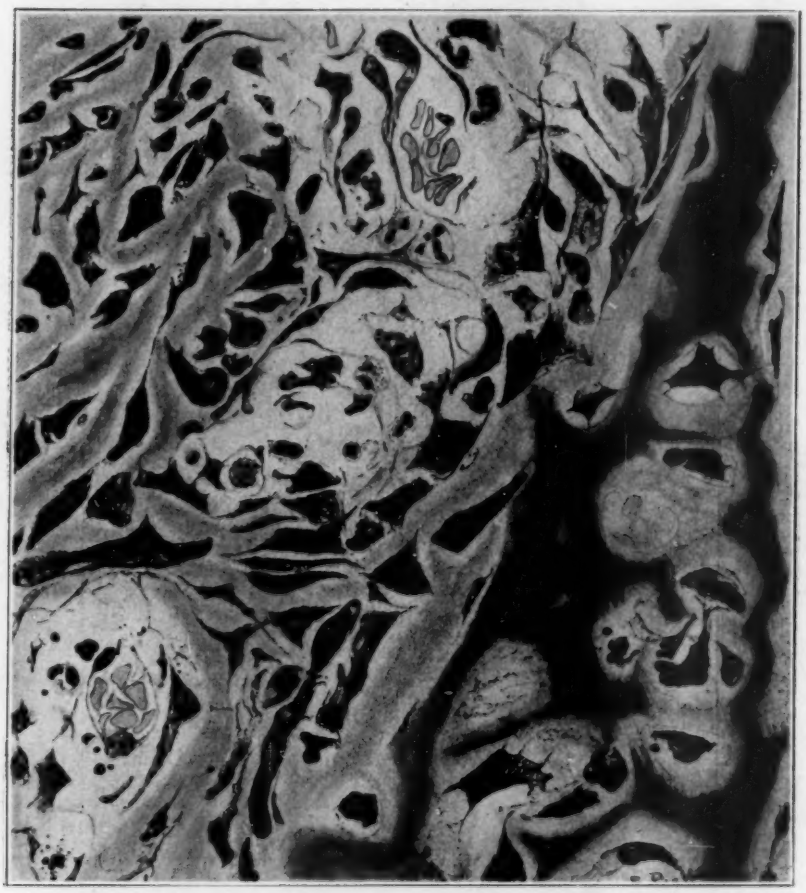

Fig. 11.—Costochondral junction of a guinea-pig after fourteen days on the scorbutic diet and three days with the addition of orange juice. Killed three days after the first administration of orange juice. There has been a deposit of bone matrix between the cells of the gerüstmark, thus proving the osteoblastic origin of the cells. × 675.

tous or myxomatous in appearance. This loose texture we believe to be caused by the presence of a liquid intercellular material. The cells have all the appearance of fibroblasts, including fibroglia fibrils. Red blood corpuscles, possibly by diapedesis, are frequently present between the

cells of this gerüstmark. The blood corpuscles do not undergo phagocytosis. They become enveloped in a material the nature of which is disputed. Aschoff and Koch have called it fibrin. Höjer, discussing it at length, called it bone. This material if fibrin would seem too abundant to have accompanied the number of red corpuscles present. As hemosiderin is a product of phagocytosis, the absence of pigment is of no importance in the discussion. Strands of fibrin are present in this material and stain densely blue with the phosphotungstic acid hema-

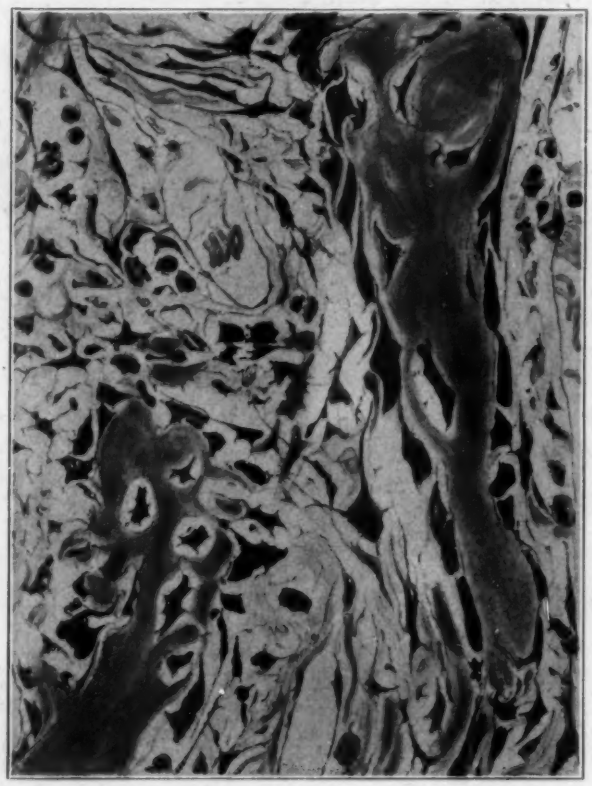

Fig. 12.—Costochondral junction of a guinea-pig after twenty-five days on the scorbutic diet followed by the addition of orange juice for six days. Killed six days after the first administration of orange juice. Bone trabeculae have formed in the gerüstmark; resorption of some of the newly formed bone matrix is in evidence. × 540.

toxylin stain. In addition to the fibrin, there is a homogeneous light brownish staining matrix comprising this material. The most abundant deposit of this fibrin and matrix was found adjacent to the cartilage after the nineteenth to the twenty-third day. Its occurrence coincided with the period of rapid dissolution of cartilage preceding and causing the infractions so common in scorbutus.

Our explanation is that this material has as its basis a product of the cells of the gerüstmark, probably liquid until added to by materials from blood plasma or cartilage matrix resorption. The amount of fibrin varies, but it is always considerable after infraction. We cannot agree with Höjer that it is of the nature of bone matrix, because following antiscorbutic treatment we found bone matrix deposited about this material.

The dissolution or resorption of cartilage columns, which we have constantly observed during the third week, was followed in the fourth

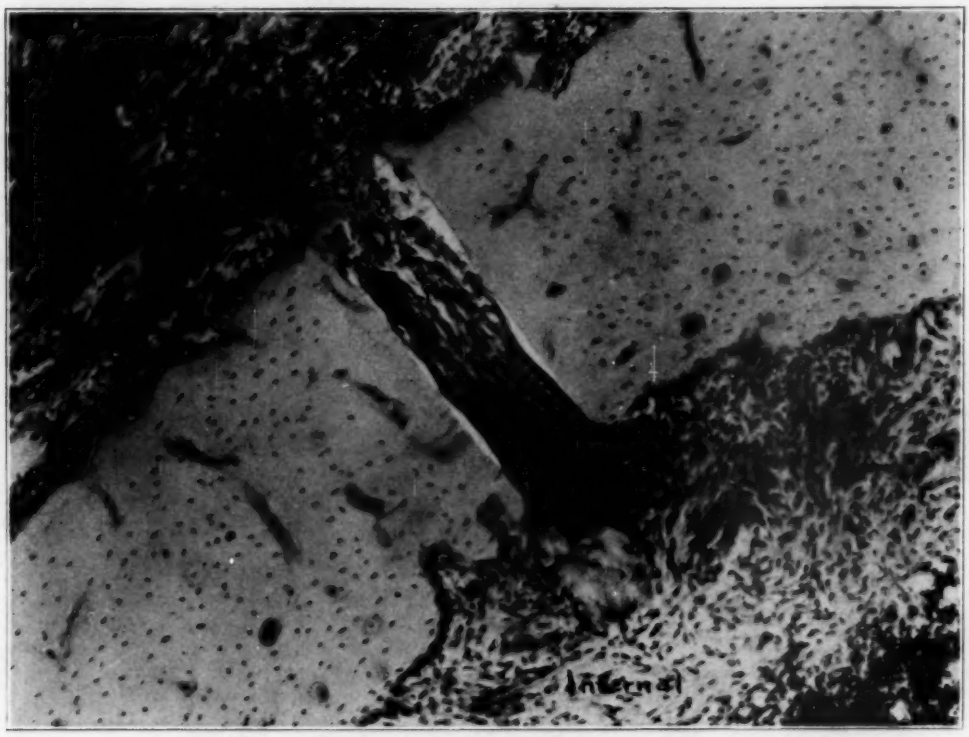

Fig. 13.—Incision of shaft of femur. Operation on tenth day on scorbutic diet. The guinea-pig was killed at the end of six days. In this instance there was only slight damage to the marrow, so that the bone defect has filled with fibroblast-like cells unaccompanied by capillaries and without intercellular substance. × 300.

week by a similar process in the cartilage distal to the costochondral junction. This breaking down of the cartilage matrix begins in the center of the rib, and results in a cavity without cells filled with basic staining granular material.

The administration of orange juice after extensive building of gerüstmark was followed promptly by the deposition of bone matrix

between the fibroblast-like cells. This was a diffuse process, as seen at the end of three days' treatment with orange juice (fig. 11). By the sixth day there was a definite structure or architecture of osteoid and osseous trabeculae, between which we found evidence of resorption of some of the bone matrix first laid down (fig. 12). Percisely analogous sequences occurred simultaneously in the periosteal new bone formation. We did not carry our studies over a sufficient period to follow the slower reparative responses of cartilage.

We may summarize the effects of the scorbutic state on growing bone by the statements that the production of the matrix of bone ceases and that maintenance of existing bone matrix is interfered with, as shown by the osteoporosis. The appearance of the gerüstmark and the sequences following antiscorbutic treatment are best interpreted in the light of the sequences observed in the teeth to the effect that the osteoblasts continue to produce a defective product, liquid in nature. The proliferative activities of the osteoblasts are not diminished, and probably are augmented over a considerable period of time.

SEQUENCES IN THE REPAIR OF SOFT TISSUES

Two experiments furnished material for the study of repair by organization.

One experiment was that planned for the study of the repair of bone injury. Twelve guinea-pigs all weighing between 160 and 190 gm. were kept on the deficient diet for ten days. On the eleventh day, under ether anesthesia, the left femur of each was exposed, and a thin slit parallel to the long axis was sawed through the cortical bone by means of a small rotary dental saw 0.09 mm. thick driven by a dental engine. The wound was closed by skin sutures only. After the operations, six of the guinea-pigs were kept on the deficient diet, and six were given 8 cc. of orange juice and a liberal supply of lettuce daily in addition to the scorbutic diet. We thus had the opportunity to follow repair in scorbutus and under the influence of antiscorbutic treatment at the same time intervals. One guinea-pig of each set of six was killed at the end of two, four, six and nine days when it became apparent from the gross observations that the period of important sequences had passed.

The other experiment began with guinea-pigs from 400 to 600 Gm. in weight after twelve days on the scorbutic diet. The operation was devised with the intention of following repair of cartilage and the process of filling a defect by organization. The operation consisted in cutting a wedge-shaped piece from the ensiform, exposed and pulled into view through an incision made over the lower end of the sternum. After removal of the piece the ensiform cartilage was allowed to slip

back into position and the skin and muscle were sutured. We followed the repair at three, six and ten day intervals in guinea-pigs kept on the deficient diet and in those treated with orange juice and lettuce as in the first experiment.

In the first experiment, slight gross differences only were noted in the healing of the skin incision. All of the wounds remained dry, and there was no sloughing. The crust over the skin incision remained longer in the animals on continued scorbutic diet. In the second experiment, no difference was noted in gross until the sixth day, after which the wounds of the guinea-pigs on continued scorbutic diet showed evidence of failure to heal somewhere along the line of incision. By the tenth day the wounds of those on antiscorbutic diet were completely healed, while two remaining on the scorbutic diet presented ulcers, one discharging pus, the other dry and crusted.

The material from the first experiment was fixed in Zenker's fixative and was embedded in celloidin after decalcification in 5 per cent nitric acid. That from the second experiment was similarly fixed, but was embedded in paraffin without having been treated in nitric acid, so that fine details could be followed and special stains applied. Mallory's connective tissue and phosphotungstic acid hematoxylin stains were of great value in following and contrasting the formation of collagen in the treated and untreated guinea-pigs.

The Epidermis.—We could detect no difference in either experiment between the treated and untreated guinea-pigs as regards the regenerative activities of the epidermis. In the guinea-pigs kept on the scorbutic diet, the epidermis responded as promptly as in the controls, and when apposition was poor, covered the cut surfaces of the corium by down growth and massing of cells. In every instance in the first experiment the epidermis completely covered the wound and bridged over gaps filled with blood and fibrin into which fibroblasts had penetrated, but in which there was no blood vessel formation. In fact, owing to failure of organization of the defect in corium and deeper tissues, the products of epithelial proliferation were greatest in the animals kept after operation on the scorbutic diet.

Cartilage.—In the second experiment there was complete absence of reparative activity on the part of the ensiform cartilage in the guinea-pigs of both sets—those kept on scorbutic diet and those receiving antiscorbutic treatment following the operations.

Mononuclear Phagocytes.—In both experiments we found no difference in the activities of mononuclear phagocytes (endothelial leukocytes) in the reaction to various types of material. Foreign body giant cells appeared as promptly in guinea-pigs kept on scorbutic diet as in those

receiving treatment, and were present in the first experiment in both sets forty-eight hours after the operation, in response to bone fragments, fat crystals and degenerated tissue elements.

Skeletal Muscle.—The durations of both experiments were too short to follow to the end reparative sequences in muscle. As far as the early stages of regeneration of injured muscle fibers, there were no differences. Multiplication of nuclei of the sarcolemma was as prompt in occurrence and as voluminous in untreated guinea-pigs as in the treated.

Repair by Granulation.—In both experiments we could find no difference between treated and untreated guinea-pigs in the promptness and volume of fibroblastic proliferation, though striking contrasts were present in collagen formation and in growth of capillaries. In the guinea-pigs receiving antiscorbutic treatment after operation, organization by fibroblast and vascular ingrowth proceeded in normal fashion.

In the second experiment as early as the third day following operation in the guinea-pigs receiving antiscorbutics, there was new capillary formation. Fibroblastic proliferation was active, and collagen had been formed by cells which had penetrated fibrinous exudate and blood clots. In the companion guinea-pig kept on the scorbutic diet, fibroblastic proliferation and migration were equally active, but there was no trace of collagen formation and no new capillary formation. Efforts toward capillary formation were evident in capillaries and vessels of precapillary size in fat tissue adjacent to the operative defect in that endothelial cell mitoses in situ were numerous and because endothelial cells accumulated in the lumina of these vessels and outside of them as clumps or buds without arrangement.

In both experiments in the guinea-pigs kept on the scorbutic diet healing proceeded by avascular organization. Fibroblasts penetrated the defects filled with blood clot or fibrin and continued to divide by mitoses. These fibroblasts in some instances produced no demonstrable collagen; in other guinea-pigs, notably those with the bone operation, a small amount of collagen was deposited, so that by the ninth day following operation a cellular cicatrix resulted in which only traces of collagen could be demonstrated. The fibroblasts in this repair in complete scorbutus have easily demonstrable fibroglia fibrils, a fact strongly indicative of a chemical composition unlike that of collagen.

In both experiments for the study of repair, sections of the skull were also made through the incisor teeth from each guinea-pig. The study of these sections brought to light the interesting fact that in the guinea-pigs kept on the scorbutic diet, some new formation of dentin followed the operation. This interruption of the sequences in the progress of absolute scorbutus proves that antiscorbutic materials are

liberated in the destruction of tissue. Therefore the formation of collagen by fibroblasts in the repair of soft parts injured in the bone operation procedure may be accounted for, in part at least.

SEQUENCES IN THE REPAIR OF BONE INJURY

In the guinea-pigs with antiscorbutics added to their diet after the operation, described above, repair of the bone defect proceeded with rapidity. At the end of the fourth day the gap was filled by fibro-

Fig. 14.—Same as figure 13 but ten days following the operation, scorbutic diet continued. There is almost no repair. The bone defect is invaded by a few spindle shaped cells. On the external surface is shown the fibrin-like substance discussed in the text. × 300.

blast-like cells accompanied by capillaries. The formation of an internal callus was in progress, and osteoblasts had begun to deposit bone matrix on the cut edges of the bone, extending outward from the internal callus (fig. 15). At the end of the sixth day, we found abundant external and internal callus formation and the defect nearly filled with new bone matrix incorporating a single row of osteoblasts on each side of the gap. New bone was separated from the cut edges of old bone by a thin line of

finely granular material, probably derived from fibrin but now staining bluish with Mallory's connective tissue stains, purplish with hematoxylin and eosin.

At the end of nine days, the new bone has practically filled the gap. Several rows of osteoblasts are incorporated on each side of the gap in the new bone. New and old bone are still sharply demarcated, evidence we believe in attributing the sole source of bone formation to osteoblasts from endosteum and periosteum (fig. 16).

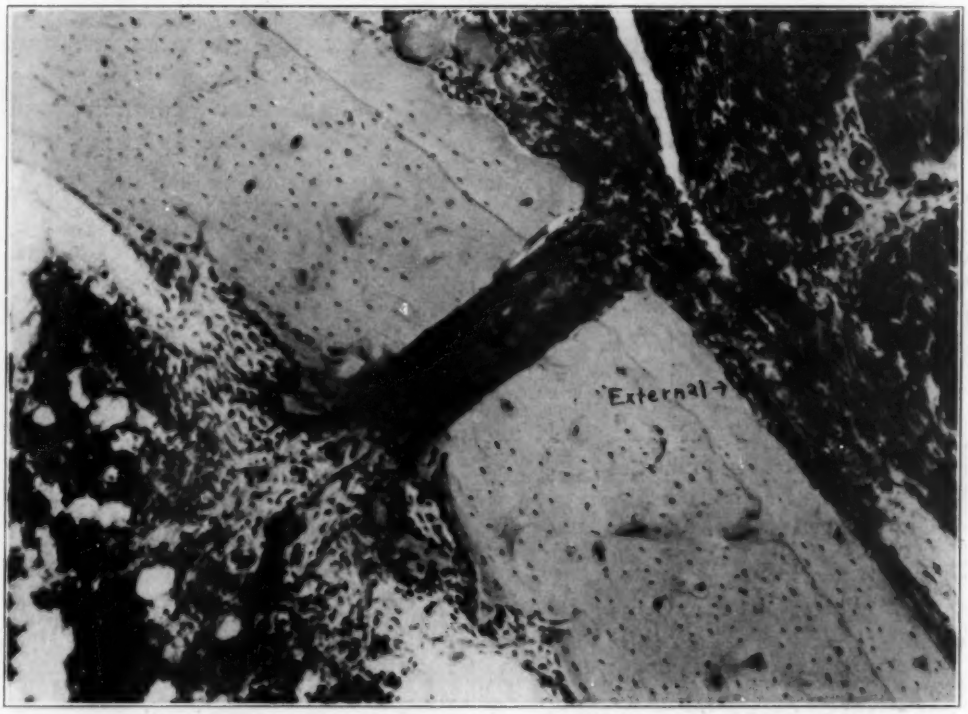

Fig. 15.—Incision of shaft of femur. Operation on tenth day on scorbutic diet, continued for four days with the addition of orange juice. The guinea-pig was killed four days after the first administration of orange juice. There is an early internal callus formation. The bone defect is filled with cells, presumably chiefly osteoblasts accompanied by capillaries. × 300.

In marked contrast, in the guinea-pigs kept on the scorbutic diet no new bone formation is found at the conclusion of the experiment at the end of the ninth day after operation. In the guinea-pig killed seven days after the operation the gap in the bone was filled with fibroblast-like cells without trace of collagen and unaccompanied by capillaries (fig. 13). This avascular organization was possible in the animal because the cut was sawed with minimum injury to the marrow. In the other untreated

guinea-pigs there was no repair of the bone gap. At the end of nine days, we found the defect in the bone filled with blood corpuscles and fibrin penetrated by a few fibroblast-like cells. Cells having the appearance of osteoblasts were absent, and there was no suggestion of bone matrix formation (fig. 14).

The soft tissues external to the bone react as has been described in the account of healing of soft tissue. After six days, we found a homogeneous fibrin-like material in immediate contact with the bone similar to that which we discussed in our account of the sequences in

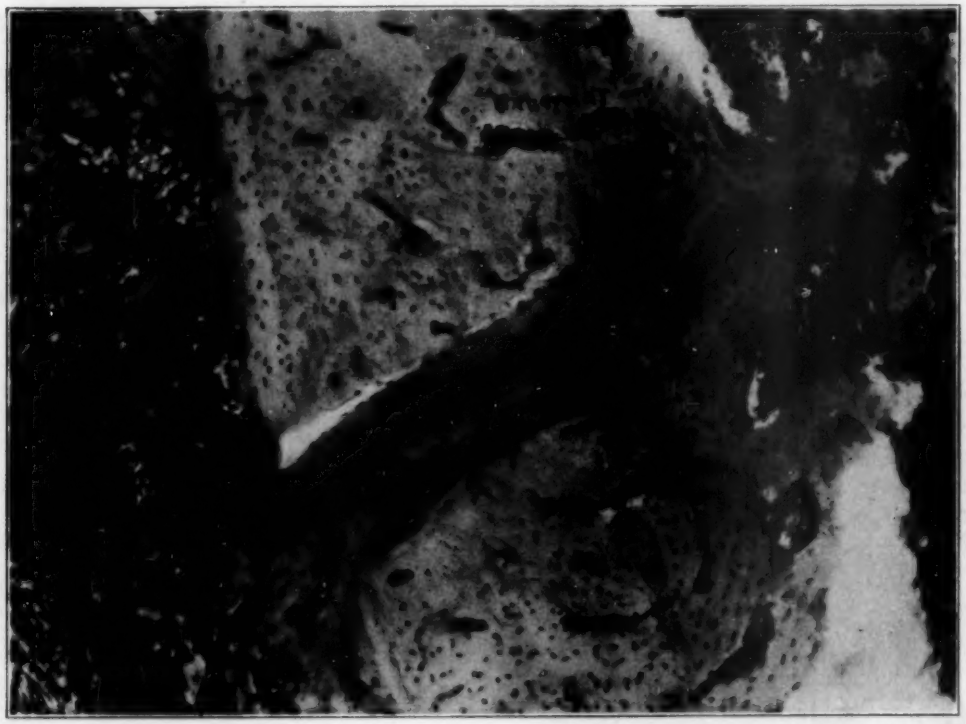

Fig. 16.—Same as figure 15 but ten days following the operation; orange juice addition to scorbutic diet. The bone defect is nearly filled with newly formed bone; there are well developed internal and external callus formations. × 300.

growing bones and which is found at epiphysial lines and costochondral junctions. It was called fibrin by Aschoff and Koch and homogeneous bone by Höjer. This material, although containing fibrin threads, consists of a homogeneous matrix already noted as staining brownish with phosphotungstic acid hematoxylin. With Mallory's connective tissue stain it takes the blue coloration, and I repeat our opinion that this material is an intercellular product jelled or set by material derived from injured tissues or blood plasma.

In the marrow the injury caused by the saw cut is followed by avascular repair. The cells derived both from fibroblasts and from endostial osteoblasts form no intracellular material except where they are in contact with fibrin or dead tissue, and here again we found the local production of the peculiar matrix under discussion.

This experiment showed complete absence of repair of bone in scorbutus other than by avascular organization without formation of collagen or bone matrix, and gives additional evidence that the fundamental condition in scorbutus is the failure of cells to form intracellular material.

SUMMARY AND CONCLUSIONS

We have described the morphologic concomitants of the condition of complete scorbutus and the immediate responses in repair. Our work establishes the hypothesis of Aschoff and Koch and confirms some of the observations of Höjer, although our methods of procedure and resultant material give us few points of contact.

We characterize the condition of scorbutus as inability of the supporting tissues to produce and maintain intercellular substances. Direct proof of this conclusion has been obtained in study of teeth in regard to dentin, in the study of growth and repair of bone in regard to bone matrix and in the study of repair of soft tissue in regard to the collagen of connective tissues. Our proof in regard to cartilage is incomplete.

The failure of capillary formation can be explained reasonably in the light of knowledge of other intercellular substances as due to failure of endothelial cells to form cement substance, an inference that Aschoff and Koch arrived at. We have at least shown that proliferative activity of the vascular endothelium is not at fault.

The proliferative power of epidermis, endothelium, fibroblasts and osteoblasts is not diminished in scorbutus. We are reasonably certain that it is augmented in the case of osteoblasts, which, however, undergo striking morphologic change.

Study of the sequences following antiscorbutic treatment has enabled us to control our observations at every stage in regard to the nature of cells contributing to the histologic ensemble of scorbutus. Osteoblasts, in spite of the great change in morphology, with complete similitude to fibroblasts, preserve their chemical potentialities and produce bone matrix.

Study of the sequences in teeth in progressive scorbutus, namely, the separation of the odontoblast layer from the dentin, led us to the theory that these cells continued to produce a liquid material. The same theory accounts for the edematous appearance of the fibrous-tissue-like structure in bones called gerüstmark. The theory as a whole is supported by the promptness and volume of matrix formation following antiscorbutic treatment.

We therefore advance the theory that the failure of cells to produce intercellular substance in scorbutus is due to the absence of an agent common to all supporting tissues which is responsible for the setting or jelling of a liquid product. Antiscorbutic substance is liberated in the destruction of tissues. The osteoporosis suggests further the hypothesis that this reaction is in some degree a reversible one.

We hope that the observations recorded in this report may suggest an approach to the study of the physiology of intercellular materials.

AMYLOIDOSIS PRODUCED BY INJECTIONS OF PROTEINS *

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The production of experimental amyloidosis in mice by repeated intramuscular injections of sodium caseinate (nutrose), which was first described by Kuczynski,[1] yields new possibilities for studying this interesting pathologic process. Previous to Kuczynski's work, amyloidosis was generally considered as being due to protracted infections and intoxications. This was in accordance with observations in human pathology, and with the results of earlier experiments in which amyloid degeneration had been observed following the injections of living or dead bacteria, or of bacterial toxins (Bailey [2]).

In attempting to explain his findings, Kuczynski assumed that the flooding of the body with foreign proteins caused the formation of abnormal intermediary products of the disturbed protein metabolism. These products dissolved with difficulty, and were precipitated from the supersaturated tissue fluids, thus forming the amyloid substance.

Kuczynski states that many injections of nutrose are necessary to secure positive results. By means of injections of bacteria, amyloid degeneration in mice can be produced in a much shorter time than with the caseinate, of which at least forty injections are required (Kuczynski, Strasser [3]).

RELATION BETWEEN AMYLOID DEGENERATION AND NUMBER OF PROTEIN INJECTIONS

In order to obtain exact information as to the number of injections that lead to the process of amyloidosis, a series of mice received daily injections with different amounts (0.2 to 1.0 cc.) of nutrose (Pfannstiehl). A 3 per cent. solution in physiologic sodium chlorid was prepared freshly every day, sterilized by boiling for five minutes and injected as sterile as possible alternately into the muscles of the left and right hind leg. The local reactions were slight. Aerobic and anaerobic

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1. Kuczynski: Virchows Arch. f. path. Anat. **239**:225, 1922; Klin. Wchnschr. **2**:722, 2193, 1923.

2. Bailey: J. Exper. Med. **23**:773, 1916.

3. Strasser: Ztschr. f. d. ges. exper. Med. **36**:381, 1923.

cultures of the muscles were made after the animals had been killed, and these always remained sterile.

The results of these experiments are summarized in the table.

It appears from this table that certain individual differences exist regarding the disposition to amyloid degeneration when less than sixty injections are given. After about sixty injections, the results become uniform, amyloidosis being found in all animals receiving injections. At that time the amyloidosis may still be confined to the spleen, and a general amyloid degeneration is not constantly observed until eighty injections have been given.

If Kuczynski is right in stating that amyloidoses results from the flooding of the body with the products of an abnormal cleavage of foreign protein, we should expect a dependence of the degenerative processes on the amount of protein that is injected. Larger amounts should hasten the development. This, however, is not true. When

Results of Experiments on Mice

Number of Mice	Number of Injections	Spleen	Liver	Kidney	Supra-renal	Intestine, Lymph Glands, etc.
10	Less than 40	2	2	0	0	0
10	40-55	5	3	3	2	2
10	56-70	10	5	5	3	3
10	71-85	10	8	8	8	6
10	86-100	10	10	10	10	10

1 c.c. of the solution is given (the largest amount which can be injected into the leg of a mouse without causing severe damage), the same number of injections are required as when 0.2 cc. is used.

The question arises as to what the causal relation might be between the number of injections and the tissue alterations that lead to the formation of the amyloid substance. Casein and its easily soluble sodium salt are primarily not toxic. They cause slight reactions when introduced parenterally for the first time. This is the reason why casein has frequently been used in foreign protein therapy. Also, the mice do not seem to be affected by the injections of the caseinate during the first four to eight weeks. They gain in weight, and do not differ from the normal controls.

CHANGES OF BODY WEIGHT

Between the fifth to tenth week, the weight suddenly starts to drop, and goes down gradually to a level below that at the beginning of the experiment. Some of the mice died after from sixty to eighty injections, some survived as many as ninety to one hundred.

The change in the behavior of the body weight is a reliable indication of the presence of amyloidosis. The beginning of the decrease

in weight precedes the onset of the degenerative changes from one to two weeks. When a mouse was killed while its weight was still going up, or had remained unchanged for a few days, amyloidosis was absent. When a mouse was examined that had lost weight during the last seven to fourteen days, amyloidosis was always found.

These observations suggest that the reaction of the organism to the foreign protein changes during the course of the injections and the nutrose, harmless for a certain period of time, finally becomes injurious. The changes in the body reactions that follow repeated injections of foreign protein have been studied by many investigators. and special attention should be called, in this connection, to the work by Schittenhelm and Weichardt.

CHANGES IN BLOOD PICTURE

The microscopic examination of the blood supports this assumption. The mice develop a slight anemia after from forty to sixty injections. The number of the erythrocytes goes down from 7½ millions to 5 millions; the hemoglobin decreases from 110 per cent. to 80 per cent.

Pentimalli [4] described a hypochromatic anemia with leukocytosis in chronic protein poisoning of rabbits. Leukocytosis was also present in the mice receiving injections with nutrose. The leukocytosis, however, showed no relation to the onset or development of the amyloid degeneration. During the first weeks the white cells went up from 8,000 to 15,000 or 18,000; later their number remained more or less stationary, and in only a few mice was it finally above 20,000. The leukocytosis was due to an increase of the neutrophil leukocytes. Whereas in normal mice from 10 to 15 per cent. of the leukocytes are neutrophil granulated, their percentage in the mice that had received the nutrose solution amounted to from 40 to 50 per cent. The lymphocytes showed a corresponding decrease. The monocytes increased from 5 per cent to 8 or 10 per cent. The eosinophil leukocytes were not changed (1 to 2 per cent). Myelocytes were absent, and granulocytes with ring-shaped nuclei were the only less mature cell types found.

CHANGES OF TEMPERATURE REACTION [5]

Interesting results were obtained in recording the changes of the body temperature caused by injections of the caseinate. The injec-

4. Pentimalli: Klin. Wchnschr. **3**:2090, 1925.

5. The rectal temperature was taken. In order to secure reliable results, it is necessary for the mice to become accustomed to this procedure, otherwise the temperature may change because the animal is frightened. The rectum must be emptied before inserting the thermometer, which is allowed to remain in the rectum for from two to three minutes. Mice with bronchopneumonia (evident from an abnormal temperature) must be discarded.

tion of nutrose into a normal mouse is followed by a rise in the temperature, amounting to from 1½ to 2½ F., which reaches the maximum after from two to four hours. During the next two to four hours the temperature returns to normal (99 to 101 F.). With the increase in the number of injections, the rise in temperature becomes less and less pronounced, and after six or seven weeks, when a drop in the body weight is noted, the nutrose does not cause the temperature to rise, but, on the contrary, a decrease in temperature is now noted. The decrease is slight, its average being 2 F. This type of temperature reaction persists. In some of the mice, especially in those that had received very many injections, the temperature was found to be continuously lower than normal. In the morning, even before the injections were given, the temperature was from 2 to 3 F. below normal. The injection was either followed by a further decrease to 95 F. or less, or the temperature remained almost unchanged. Examination of these mice revealed extensive general amyloidosis.

Decrease in the temperature, according to Pfeiffer, points toward the toxic action of abnormal split products of the body proteins. Destruction of body tissue resulting from burning, photodynamic action of light, injection of trypsin, etc., leads to a sudden drop in temperature, which continues until the death of the animal. Application of heat (warm-box) may save the injured animal (Pfeiffer [6]).

The decrease in temperature and the decline in body weight that occurs after repeated injections of nutrose seem to indicate that the caseinate stimulates an abnormal toxic cleavage of body tissues in the sensitized mouse. The effect of the single injections is slight, but it is the frequent repetition of the irritation that finally becomes harmful. For a long time it has been known that amyloidosis results from protracted destruction of body tissues. There is no fundamental difference as to pathogenesis between the amyloidosis produced by the nutrose injections and that encountered in chronic infections and intoxications, since in all these conditions an abnormal breakdown of tissue apparently takes place.

EXPERIMENTS WITH SERUM

The question may arise as to whether the amyloidosis is confined to the action of the nutrose or whether other proteins may have a similar effect. To decide this question, a second series of mice received injections with fresh sterile human serum. The injections were given in the same way as those of the caseinate. These mice also gained in weight at first. A decline was again noted after the fortieth to sixtieth injection. When killed before this decline had started, no amyloid was found.

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6. Pfeiffer, H.: Ztschr. f. d. ges. exper. Med. **29**:46, 1922.

During the sixth to eighth week, however, amyloid appeared first in the spleen, then in the liver, kidneys, suprarenals, lymph glands, etc. The same findings were obtained by using animal serum.

The amyloidosis that occurs after long continued injections of nutrose, human serum, etc., can therefore be considered as the result of a chronic protein poisoning; and it is typical of the mouse, an animal especially disposed to this form of degeneration.

MORPHOLOGY

The amyloid is first found in the spleen. In the earliest stages, it surrounds the malpighian bodies as bands; later, the pulp may be completely replaced by a coarse framework of amyloid. The luminae of the sinuses still exist, but their endothelium has disappeared, and the small amount of blood which they contain borders on amyloid.

The second organ to be involved is the liver; then the kidneys, suprarenals, lymph glands and intestines become involved. The changes finally become so extensive that almost every tissue, except the skin, the central nervous system and the sympathetic ganglions, is affected. The amyloidosis is much more pronounced than that observed after injections of bacteria, or that caused by the growth of transplantable malignant tumors. Thus, the kidneys, after many injections of the protein, showed the characteristic macroscopic picture of the third stage of the amyloid nephrosis. Their surface was covered with coarse granules, consisting of distended tubuli. In the depressions between the granules, a complete amyloid transformation of the glomeruli, with atrophy of the tubuli and proliferation of the interstitium, was found.

In the pancreas, amyloid was present, especially about the capillaries of the islands. Two localizations will be described more in detail, because they have not so far been recorded in experimental amyloidosis. In the heart, amyloid is not only deposited about the vessels of the myocardium, but it is also found in the leaflets of the valves, mainly in that of the valvula mitralis. Here it is located near the auricular surface as a compact layer, which becomes paler toward the middle of the valve, and it stands out distinctly against the valvular tissue proper (fig. 1).

In the ovaries, amyloid is observed in the walls of the vessels, and in the corpora lutea. The deposits are so extensive that the corpora lutea appear as circumscribed amyloid tumors (fig. 2). The lutein cells are shrunken, contain little lipoid, and their nuclei are pyknotic.

The amyloid produced by protein injections gives the microchemical reactions typical of this substance. It is necessary, however, for the fresh tissues to be fixed with 85 per cent. alcohol. It has often been stated that in experimental amyloidosis the metachromasia with gentian

or methyl-violet is the only reaction which is distinct, the characteristic coloring with iodin or iodin sulphuric acid being absent, or much less pronounced (Bailey). The freshly deposited amyloid, in particular, is said to react only with the anilin dyes (Schmidt,[7] Davidsohn, and others).

In the experiments with nutrose and serum, the first traces of amyloid give a reaction with iodin at a time when the metachromatic coloration with methyl-violet is still hardly visible. The amyloid, when treated with iodin, has, however, a different color than the amyloid in the human

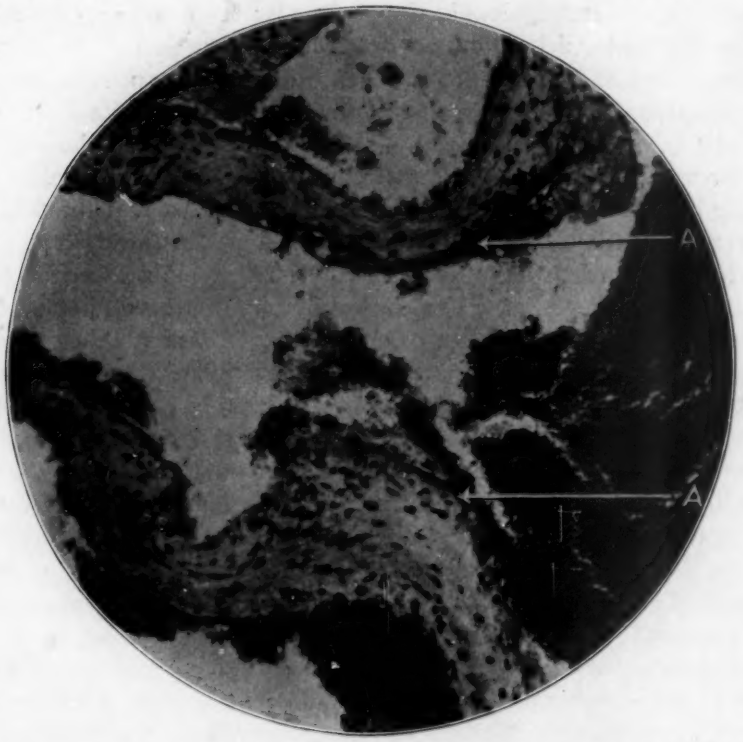

Fig. 1.—Amyloid (*A*) in the leaflets of the mitral valve. Ten per cent. liquor formaldehydi Hemalaun-eosin stain; × 160.

tissues. It stained pink, and this color persisted and never turned mahogany brown, which is typical of the human amyloid. The addition of sulphuric acid changed the pink color to grayish blue or a pale green.

In the sections stained with methyl-violet the amyloid appeared bright purple. When methyl-green was used, it stained reddish violet.

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7. Schmidt, M. B.: Virchows Arch. f. path. Anat. **254**:606, 1925.

With Congo-red (Bennhold [8]), the amyloid took up only a pale pink, and the brilliant red of the human amyloid was never observed.

The crystalline structure of the amyloid that Kuczynski describes is characteristic. Crystal-like bristles of amyloid were first observed by Maximow [9] in the horse liver. Domagk [10] found needles of amyloid in the liver of mice that had received large amounts of bacteria cultures. Similar observations were made in mice with tumors (Kuczynski). In

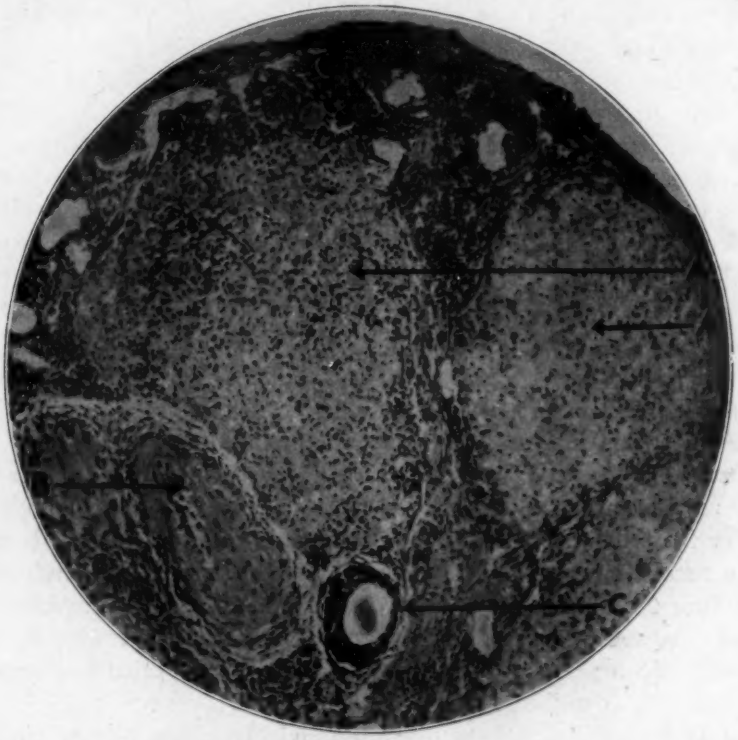

Fig. 2.—Amyloid degeneration of corpora lutea of ovary. *A* indicates amyloid in the corpora lutea; *B*, amyloid in the wall of an artery; *C*, Graafian follicle. Eighty per cent. alcohol. Hemalaun-eosin stain; × 110.

other animals and in human beings the amyloid does not show this morphology.

The formation of the finest needles by the amyloid substance is not restricted to the liver. The tufts of the amyloid needles are found in most of the organs affected. Fixing with Zenker-Helly solution

8. Bennhold: München. med. Wchnschr. **69**:1537, 1922.
9. Maximow: Virchows Arch. f. path. Anat. **135**:353, 1898.
10. Domagk: Virchows Arch. f. path. Anat. **253**:594, 1924.

and staining with Mallory's anilin-blue method brings out these structures most distinctly.

The first deposits of the amyloid appear as fine membraneous foils at the basal membranes of the capillaries and at the reticular fibers. Cloudy masses about these membranes later become visible, and the needles differentiate out of the cloudy masses. They tend to arrange themselves radially about a more compact center, formed by a nodular thickening of the membrane or by a small cluster of disintegrated cells.

The stars and whirls of crystalline amyloid occupy the space between capillary wall and liver cells (fig. 3).

In the corpora lutea of the ovary, whirls of long needles are most distinct. In the spleen the needles are less discernible, because the peripheral parts of the brushlike trimmings of neighboring sinuses are interlaced with each other. In the kidneys, needles are seen on the inside of the basal membranes of the tubuli recti. In the glomeruli, the amyloid has a longitudinal fibrillation. The suprarenals show glittering bristles between the cortical cells and the capillary walls. The finest and shortest crystals are found on the surface of the reticular fibers of the lymph glands.

The needles cause no active cellular reaction in the surroundings, except in the liver. In this organ, proliferation of the Kupffer cells is noted after the injections have been continued for a very long time (from 90 to 100). The cells invade the crystalline clusters, destroy their regular shape, breaking up the stars and tufts into irregular débris. Under the influence of the proliferating histiocytes, the amyloid passes away, and is finally completely dissolved. In other places the endothelial cells fuse together in large giant cells, from 35 to 50 cc. in diameter, which phagocyte the amyloid crystals. By intracellular digestion the crystals lose the specific staining qualities, become paler and smaller, until only shadow-like remnants are left (fig. 4).

It is interesting to note that the amyloid in the liver is removed while the injections are continued, since the statement is usually made that the amyloid is resorbed only after the injury has been eliminated (Dantschakow,[11] Kuczynski).

In the other organs, however, endothelial resolution of the amyloid takes place only after the injections have been discontinued. That indicates that a special functional activity in the reticulo-endothelial system should be ascribed to the Kupffer cells.

The microscopic examination in the area of injections did not reveal significant changes. Amyloid, especially, was not found. There were very small groups of degenerated leukocytes surrounded by strands of

11. Dantschakow: Virchows Arch. f. path. Anat. **187**:1, 1907.

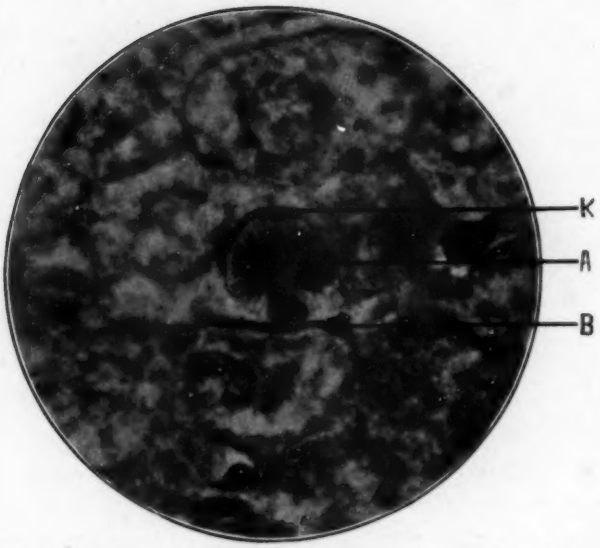

Fig. 3.—Crystal-like amyloid deposit (*A*) in the liver. *K* indicates Kupffer cells attached to the amyloid star. The wall of the capillary opposite the star shows a fine line of amyloid with a nodular thickening to the right (*B*). Zenker-Mallory's anilin-blue stain; × 750.

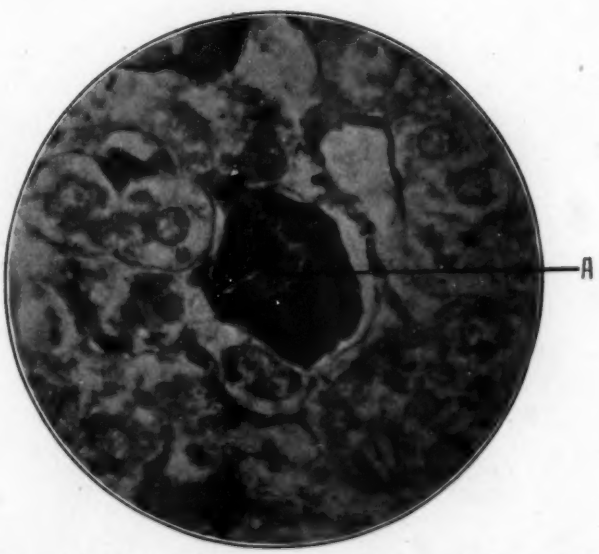

Fig. 4.—Large giant cell (*A*) in a portal capillary containing irregular masses of amyloid. Zenker-Mallory's anilin-blue stain; × 560.

scar tissue containing blood pigment, and a great many mast cells. The muscle fibers between the scar tissue showed fruitless attempts at regeneration by the formation of multinucleated buds.

COMMENT

The observation that amyloidosis results from repeated injections of foreign proteins has been explained on the basis of an acquired hypersensitiveness to the substance injected, causing an abnormal cleavage of body tissue. The nature of the protein that is used is less important than the number of the injections. The allergic stage, which is reached after about forty injections, is evident from the different type of the temperature reaction which follows the parenteral administration of the protein and from the sudden drop in weight.

Many observations prove that sensitized cells may respond to a renewed specific irritation with exhaustion and disintegration. In the experiments under discussion, microscopic signs of cellular alterations are visible. In the spleen, for instance, the giant cells greatly increase in number during the first weeks of the injections, and later become degenerated. Their protoplasm is homogeneous or vacuolated. Their nuclei are pyknotic, and the cells finally break down to form irregular débris. The liver cells contain vacuoles, lipoid granules and hyaline droplets. They are sometimes diffusely hyalinic. The nuclei often appear enlarged, irregular and hyperchromatic, and the Kupffer cells are filled with fat droplets. These changes precede the amyloid degeneration.

The experiments of Domagk, who produced amyloidosis in mice by injecting intravenously large amounts of living or dead bacteria, also seem to indicate some relation between amyloid degeneration and allergic reactions. Domagk found that injections of bacteria into immunized mice were followed by an enormous phagocytosis of the bacteria through the endothelial cells of the lung, liver, etc., and by an almost immediate appearance of amyloid. In human pathology little attention has been given to a possible relation between an allergic stage acquired in the course of a chronic infection and the appearance of the amyloid substance, although amyloidosis is most frequently found in tuberculosis, in which disease the occurrence of allergic reactions has been especially emphasized.

Human cases of amyloidosis are occasionally observed in which the most careful examination reveals no distinct cause (Eppinger,[12] Freundlich,[13] Husten[14]). There are no signs of tuberculosis, of chronic

12. Eppinger: Biochem. Ztschr. **127**:107, 1921.
13. Freundlich: Med. Klin. **19**:1622, 1923.
14. Husten: Virchows Arch. f. path. Anat. **248**:450, 1924.

suppuration, of leukemia, of syphilis or of malignant tumors. Novak mentions chronic catarrhalic inflammation of the colon. Freundlich describes an extreme general icterus. Is it not possible that the cases of apparently genuine amyloidosis are similar to the experimental amyloidosis following protein injections, in that they represent the effect of a pathologic hypersensitiveness to foreign proteins resulting from an abnormal permeability of the impaired intestine, or from an insufficiency of the liver, the importance of which for protein metabolism is well known?

The large deposits of amyloid in the corpora lutea of the ovary recall that in human pathology the amyloid often shows an affinity for areas of increased or abnormal cellular activity. Askanazy [15] says that the localization of the amyloid depends partly on the kind and intensity of the function of an organ. In cases of goiter the adenomatous nodes of the thyroid are more affected than the rest of the gland (Schilder,[16] Ipland [17]). Schmidt pointed out that the newly formed inflammatory tissue is especially involved in the process of amyloidosis.

In the human skin, amyloid is found in close connection with the sweat glands and sebaceous glands, which display a great functional activity (Schilder). Tumors which have originated in the matrix of the hair may reveal local amyloidosis (Mallory, personal communication). Amyloid in the stroma of tumors has been described by Askanazy (scirrhus of the breast) and by Schmidt (adenoma of cortex of suprarenal. McCutcheon [18] observed amyloidosis of the suprarenals in a case of hypernephroma of the kidney.

Amyloid, however, may also be found in places in which the cellular activity is insignificant, as in the valves of the heart.

The question regarding the origin of the amyloid has usually been discussed from a morphologic standpoint, because this substance is characterized by its microscopic qualities, while its chemical nature is still waiting for a definite solution. A reliable and relatively simple method to produce amyloid degeneration will undoubtedly stimulate and aid new investigations of this problem, for all explanations brought forward up to the present time are of merely theoretical interest, and none of them is entirely satisfactory.

If the parenchymatous cells of the organs in which amyloid is found are the source of it, it can hardly be explained why the different cells should produce the same substance. Domagk's observations point toward the endothelial cells as playing an important rôle; but no particular

15. Askanazy: Beitr. z. path. Anat. u. z. allg. Path. **71**:583, 1923.
16. Schilder: Beitr. z. path. Anat. u. z. allg. Path. **46**:602, 1909.
17. Ipland: Frankfurter Ztschr. f. Path. **16**:441, 1915.
18. McCutcheon: Am. J. M. Sc. **166**:197, 1923.

changes in the endothelial cells have been observed in the mice receiving injections with nutrose or serum, apart from the fatty degeneration of the Kupffer cells in the liver. Endothelial cells, however, are found active in removing amyloid.

The origin from collagenous tissue (Mallory [19]) is probable. Collagenous tissue is present everywhere in the body, and the amyloid is intimately associated with it. The fibroblasts cannot be essential, because in the liver amyloid is found in the perivascular spaces between portal capillaries and liver cells, in which fibroblasts are absent. The reticular, fibrillar and membranous differentiations of mesenchymatous origin become secondarily involved. The amyloid tends to accumulate about them, and the fibrils are visible for a long time, although embedded in large amounts of the abnormal substance. Finally, there remains only the material between the fibrils and the membranes.

The blood has been regarded as containing the substances of which amyloid is formed in the tissue spaces (Kuczynski). No characteristic changes of the blood seem to precede or accompany the amyloid degeneration. In human cases the protein content of the serum, for instance, is found diminished or increased (Koref [20]). Dresel [21] tested the serum of patients with amyloidosis for the content of chondroidin sulphuric acid. He found an increase, but this increase was not specific, and was also present in patients with renal diseases. Besides, the analyses of some investigators have shown that chondroidin sulphuric acid is not a constant part of amyloid (Hansen,[22] Eppinger [13]).

Examination of the blood of the mice receiving injections with proteins did not yield any striking results. Of course, only a limited number of tests can be made with such small quantities of blood, and objections may be raised against the methods employed. However, the fact should be stated that the protein concentration of the serum determined by Dr. Kathe Dewey by means of Pulfrich's refractometer showed no characteristic changes, and that the hydrogen ion concentration was within normal limits (7.38 to 7.4).

SUMMARY

Intramuscular injections of nutrose or serum, when given over a certain period of time, have proved to be a reliable method for producing amyloid degeneration in mice.

The reactions of the mice to the foreign proteins is changed during the course of the experiment. Whereas the injections at first cause a

19. Mallory: Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914.
20. Koref: Med. Klin. **20**:1243, 1924.
21. Dresel: Klin. Wchnschr. **2**:2344, 1923.
22. Hansen: Biochem. Ztschr. **13**:185, 1908.

slight rise in the body temperature, they are later followd by a decrease in the temperature. With the change of the temperature reaction, the weight of the animals starts dropping. From one to two weeks later the first traces of amyloid become visible in the spleen.

The conclusion has been drawn from these observations that the amyloidosis occurring after long continued injections of protein results from an acquired hypersensitiveness to the injected substance.

After more than seventy injections, the amyloidosis becomes most extensive, even the valves of the heart being affected. An endothelial resorbtion of the amyloid finally takes place in the liver, even though the injections are continued.

HYPERNEPHROMA OF THYROID

WITH CLINICAL PICTURE OF EXOPHTHALMIC GOITER *

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There is evidence on hand that infectious processes can give rise to exophthalmic goiter. Tuberculous thyroiditis, acute articular rheumatism, typhus fever and syphilis may be followed by the clinical picture of exophthalmic goiter without the histology typical for this condition. The same sometimes occurs in malignant tumors of the thyroid, whether primary or metastatic. The symptoms of exophthalmic goiter are usually so pronounced that no suspicion of malignancy in the thyroid is aroused. Apparently the reaction of the organism to the disturbance of the thyroid secretion as a result of maligant involvement of the gland is far more prominent than is the reaction to malignancy itself.

The relatively rare incidence of malignant tumors of the thyroid may be seen from the tables compiled by Wilson.[1] These tables involve about 1,430 cases of malignant tumors of the thyroid reported in the world literature prior to 1921. Statistics based on a study of 74,335 necropsies show that one case of malignant tumor of the thyroid is found in about 385 necropsies.

The largest majority of malignant tumors of the thyroid seem to be of a primary character. A metastatic involvement of the thyroid is rather a curiosity, as is seen from the exhaustive statistics of Symmers, Takeyoshi and others. Among all malignant tumors giving rise to metastases in the thyroid, hypernephroma is the rarest. From the world literature only one case of a metastatic involvement of the thyroid by hypernephroma is known. It occurred in a patient, aged 74, with a bilateral hypernephroma of the kidneys.[2]

The great rarity of occurrence of suprarenal tissue in the thyroid justifies the present report.

A woman, aged 68, had had a goiter since the age of 15. It gave her no trouble until May, 1924, when she began to develop a typical picture of exophthalmic goiter. She was admitted to the University Hospital on Sept. 3, 1924. Her basal metabolic rate on Aug. 25, 1924, was "plus 80." A bilateral subtotal lobectomy was performed by Dr. Rowan on Sept. 5, 1924. Examination of the tissue removed revealed multiple circumscribed, opaque, yellowish-

* From the Department of Surgery, University of Iowa.

1. Wilson, L. B.: Malignant Tumors of the Thyroid, Ann. Surg. **74**:129 (Aug.) 1921.

2. Pistocchi, G.: Ipernefroma Surrenale Bilaterale con Metastasi Tiroidee Tumori **9**:135 (Nov.) 1922.

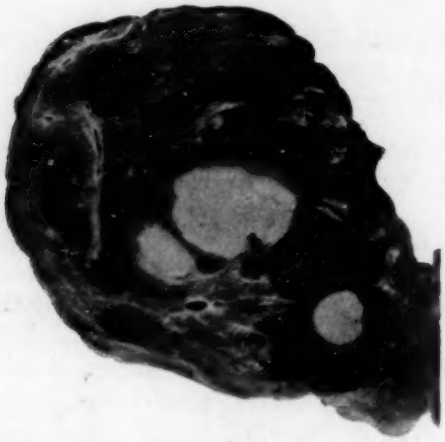

Fig. 1.—Section of the removed thyroid gland, showing the well circumscribed yellowish-white nodules.

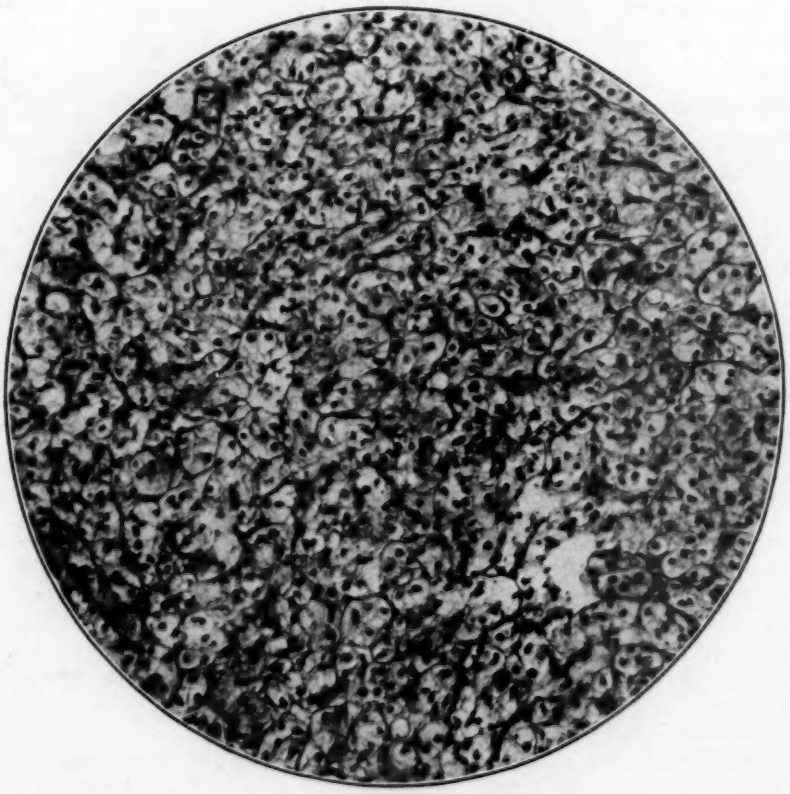

Fig. 2.—Photomicrograph of a section of a tumor nodule, showing the characteristic structure of suprarenal cortex.

white nodules, ranging in size from that of a pinhead to that of a small hickory nut.

Microscopic examination showed the nodules to be well circumscribed. They consisted of wide strands of large, clear cells anastomosing freely with one another. Abundant droplets of lipoids could be demonstrated in these cells, while no signs of degeneration could be noticed. Lubarsch's glycogen reaction was positive. In general, the tissue was a typical reproduction of the cortex of the suprarenals, and because of the multiplicity of the nodules a diagnosis of metastases of a hypernephroma to the thyroid was made.

Because of the rarity of this condition sections of the tumor were submitted to several prominent pathologists in this country. While the majority of pathologists agreed with the diagnosis made, one pathologist regarded it as a "local overgrowth of thyroid alveoli and cells with hydropic degeneration."

The positive glycogen reaction, the lipoid content of the cells and the general morphologic appearance speak well for the suprarenal origin of the tissue and against a degenerative process. The clinical picture of the condition—exophthalmic goiter—would seem to indicate that the thyroid was in a stage of active irritation and not degeneration. The thyroid tissue removed showed a moderate degree of hyperplasia with the exception of areas adjacent to the tumor nodules. Here the acini were lined with high cuboidal or cylindrical epithelium. All these factors would seem to speak definitely against any possibility of the nodules being a result of degenerative changes in the thyroid.

Two interpretations are possible of the nature of the nodules in the thyroid: One is that the nodules are an overgrowth of aberrant suprarenal tissue in the thyroid, and the other that the nodules are metastases of a hypernephroma.

The first interpretation is not as unusual as it seems. Schmorl showed that the frequency of aberrant suprarenal tissue is far greater than it is usually thought. As a matter of fact, he found these to be present in 92 per cent. of all necropsies. These aberrant residues may give rise to neoplasms. It is known, however, that the majority of aberrant suprarenals atrophy in the course of years, and therefore they are seldom found in later life. For this reason such an interpretation of the nodules of the thyroid in this case seems improbable; more so when it is recalled that all known cases of aberrant suprarenals were observed below the diaphragm. These considerations lead to the second interpretation and to the diagnosis of metastases of hypernephroma to the thyroid.

Strange as it is, a most careful general examination of the patient and roentgenoscopy of the skeleton did not help in the search for the primary tumor. After the lobectomy the patient improved markedly,

and there does not seem to be any evidence of a recurrence of the tumor in the thyroid up to the present time—eleven months after the lobectomy. It is realized, however, that this is not too long a period of time for a recurrence.

RÔLE OF ENDOTHELIUM IN THE PRODUCTION OF POLYBLASTS (MONONUCLEAR WANDERING CELLS) IN INFLAMMATION *

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Notwithstanding an extensive literature on the subject, the question of the histogenesis of the inflammatory process and, especially, the origin of the phagocytic mononuclear ameboid wandering cells is not settled. Among those who have discussed the question extensively are Marchand,[1] Maximow,[2] Rössle [3] and Foot.[4] The differences of opinion concern chiefly the rôle of the nongranulated leukocytes, the lymphocytes and monocytes in the production of the exudate cells.

The dominant idea at the present time ascribes to the nongranulated leukocytes a modest rôle in this respect. A certain amount of emigration of lymphocytes and monocytes is admitted, but the emigrated cells are believed to be incapable of progressive development.

According to the majority of investigators, the chief source of the exudate cells, "the macrophages," as they were called many years ago by Metchnikoff,[5] are the local fixed cells of the connective tissue. However, this rôle is not attributed to the common fibroblasts. It is well known at the present time that there are different types of fixed cells in the connective tissue. It is believed that the sources of the mononuclear exudate cells are, on the one hand, the "resting wandering cells" of Maximow [6] (the "clasmatocytes" of Ranvier, the "histiocytes" of Aschoff and Kiyono [7] and Kiyono [8]); on the other hand, the endothelium of the common blood vessels, to which an important rôle is attributed. Recently, Foot tried to give decisive evidence for the active participation

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* From the Department of Anatomy, University of Chicago.

* Aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Marchand, F.: Der Prozess der Wundheilung, Stuttgart, 1901; Beitr. z. path. Anat. u. z. allg. Path. **69**:1, 1921.

2. Maximow, A.: Beitr. z. path. Anat. u. z. allg. Path., Suppl.5, 1902; **34**: 153, 1903; **35**:93, 1904; **38**:301, 1905; **39**:333, 1906; Verhandl. d. Internat. med. Congr. zu Budapest, 1909.

3. Rössle, R.: Verhandl. d. Deutsch. path. Ges. **19**:18, 1923.

4. Foot, N.: J. Med. Res. **40**:353, 1919; J. Exper. Med. **32**:513, 533, 1920; 33:271, 625, 1921; **36**:607, 1922; **37**:139, 1923; Anat. Rec. **30**:15, 1925.

5. Metchnikoff, E.: L'Immunité dans les maladies infectieuses, Paris, 1901.

6. Maximow, A.: Arch. f. mikr. Anat. **67**:680, 1906.

7. Aschoff, L., and Kiyono, K.: Fol. haematol. Arch. **15**:383, 1913.

8. Kiyono, K.: Die vitale Karminspeicherung, Jena, G. Fischer, 1914.

of the endothelium in inflammation. He used the method devised by McJunkin [9]—the intravenous injection of a "colloidal" carbon suspension (Higgins India ink). The endothelium of the blood vessels phagocytizes carbon particles, whereas other cells are supposed to remain free of carbon. If, after the injection of India ink, inflammation is experimentally provoked in the same animal, the transformations of the endothelium, "labeled" with carbon, can easily be followed. The agent used to call forth the macrophages in the first series of the experiments of Foot was sterile melted agar injected subcutaneously. Under the influence of this stimulus the endothelial cells of the adjacent blood vessels, containing carbon particles in their protoplasm, were seen to separate from each other, to become free and to transform themselves into ameboid cells, typical mononuclear exudate cells or macrophages. In the following series of experiments, Foot used various other types of inflammatory stimuli; but the results regarding the active participation of the blood vessel endothelium in the formation of macrophages were essentially the same.

In Germany the school of Marchand (G. Herzog [10]) also emphasizes the active rôle played by the endothelium and the "cells of the blood vessel walls" in the production of mononuclear phagocytic exudate cells. Under this rather indefinite term, "cells of the blood vessel walls" (Gefässwandzellen), evidently different cell types can be understood: the endothelium proper, certain cells of embryonic character, adjacent to the outer surface of the endothelium, the resting wandering cells or histiocytes, etc. According to Herzog and Marchand,[11] the so-called adventitial clasmatocytes (histiocytes) are the most important elements. However, they are supposed also to originate from the endothelium.

A different opinion was expressed by Maximow.[2] During the period from 1902 to 1909, he published a series of papers on the histogenesis of inflammatory lesions. He distinguished three cell types in the field of inflammation: (1) Special granulocytes (polymorphonuclear granular leukocytes). They emigrate out of the blood vessels in the early stages of inflammation. They do not give origin to any permanent elements and sooner or later degenerate and disappear. (2) Fibroblasts—the local common connective tissue cells. They respond to the inflammatory stimulation by mitotic proliferation and form the basis of the granulation tissue. In the later stages they elaborate the collagenous intercellular substance of the scar. (3) Polyblasts—the ameboid phagocytic mononuclear exudate cells. Maximow gave this name to the macrophages of Metchnikoff, because they display during the course of the inflammatory

9. McJunkin, F.: Am. J. Anat. **25**:27, 1919.
10. Herzog, G.: Klin Wchnschr. **2**:684, 1923.
11. Marchand, F.: Haematologica **5**:304, 1924.

process a surprising amount of developmental potencies and appear in various forms, such as large ameboid mononuclear phagocytes (macrophages proper), as epithelioid cells, as multinuclear giant cells, as pus phagocytes, etc. The polyblasts, according to Maximow, have a double origin. A part arises through the mobilization of the local resting wandering cells (clasmatocytes, histiocytes) of the connective tissue; another part comes from the blood and represents hematogenous, emigrated lymphocytes and monocytes. After their emigration out of the blood vessels into the tissue, they rapidly hypertrophy and join the polyblasts of local origin in their further transformations. In the later stages they remain scattered in the scar tissue as peculiar fixed cells, the resting polyblasts, between the fibroblasts.

No evidence could be found in the experiments of Maximow of a participation of the endothelium of the blood vessels in the formation of polyblasts. The endothelium in inflammation forms new capillary sprouts; it may also proliferate and give off cells into the tissue which at once assume the characters of fibroblasts; but its elements never become transformed into ameboid cells.

Tschaschin,[12] a student of Maximow, confirmed these results in a series of experiments with inflammation in vitally stained animals. He also could find no indication of a transformation of the endothelium of blood vessels into ameboid elements.

Hence, in the presence of two clearly contradictory opinions, new experiments for the elucidation of the histogenesis of the mononuclear exudate cells became necessary. The technic of McJunkin and Foot seemed to offer the best means for following the transformations of the endothelium of the blood vessels throughout the whole inflammatory process.

The present investigation has been undertaken and conducted at the suggestion and under the direction of Professor Alexander A. Maximow in the anatomical laboratory of the University of Chicago.

MATERIAL AND METHODS

Adult rabbits were chosen as experimental animals. Five cubic centimeters of Higgins India ink, diluted with an equal amount of distilled water, was injected intravenously according to the method of McJunkin and Foot. From thirty to forty-five minutes after the first injection, foreign bodies were introduced into the subcutaneous tissue of the abdominal wall (experimental series *a*). Small (from 4 to 5 mm.) particles of sponge filled with agar and lecithin[13] were used as foreign bodies. They were prepared in the following way: Small dried bits of a thoroughly washed sponge were autoclaved together

12. Tschaschin, S.: Fol. haematol. Arch. **16**:247, 1913.

13. I received the lecithin through the courtesy of Dr. F. Koch of the Department of Physiology.

with a mixture of bacteriologic agar and lecithin in the proportion of 5 to 1. The melted agar-lecithin mixture could thus penetrate and fill the meshes of the sponge, and at the same time the whole was sterilized. After cooling, the portions of sponge were pulled out of the jelly with a sterile forceps and were introduced into the subcutaneous tissue through a small incision; the latter was closed with one or two silk sutures.

Foreign bodies saturated with lecithin-agar were used because Bergel[14] claims to have found that lipoid substances and especially lecithin have an elective positive chemotactic influence on lymphocytes.

At different time intervals after the introduction of the foreign body the animals were killed. If the interval was longer than twenty-four hours, a second intravenous injection of the same quantity of diluted India ink was given the next day. The stages obtained were three, six, twenty-four, thirty, forty-eight and seventy-one hours.

In a second series of experiments (experimental series *b*), on two successive days the animals received an intravenous injection of India ink. Immediately after the second injection 1 to 2 cc. of fresh egg yolk was injected into the subcutaneous tissue by means of a syringe with a needle of large caliber. Simultaneously 0.5 to 1 cc. of a 1:300 aqueous solution of silver nitrate was injected into the peritoneal cavity. These animals were killed ten, fifteen, eighteen and thirty hours after the injection of the egg yolk.

As we were interested in the origin of the polyblasts (mononuclear exudate cells) in acute aseptic inflammation, only early stages of the process were to be cared for.

From all animals the usual dry blood smears were prepared at various stages of the experiment. They were stained with May-Grünwald and Giemsa stain according to the panoptic method of Pappenheim.

After the animal was killed, the skin covering the foreign bodies or the place where egg yolk was injected was carefully separated and the denuded layer of loose subcutaneous tissue, together with the underlying muscle sheet, was stretched in natural position on a cork frame by means of cactus needles and fixed in warm Zenker-formol solution. Besides, from every animal pieces of liver, spleen and lymph nodes were taken. The fixed material was embedded in celloidin; the subcutaneous tissue was cut in serial sections parallel to its broad surface. The sections were stained with eosin-azure according to the method devised by Maximow;[15] recently the method has been slightly modified and improved by staining the sections previous to the eosin-azure mixture with a very weak solution of Delafield's hematoxylin for twenty-four hours. The chromatin of the nuclei acquires after this hematoxylin-eosin-azure stain a particularly deep blue color, and the slides do not fade.

Pieces of the omentum of the animals in the second series, after fixation in a stretched position, were stained in the same way as the sections, and mounted in toto.

FATE OF THE INDIA INK INJECTED INTRAVENOUSLY

If a drop of Higgins India ink—diluted with distilled water or undiluted—is placed on a slide, covered with a coverslip and focused with

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14. Bergel, S.: Ztschr. f. exper. Pathol. u. Therap. **21**:216, 1920. Die Lymphozytose, Berlin, J. Springer, 1921.

15. Maximow, A.: Ztschr. f. wissensch. Mikr. **26**:177, 1909.

a high power immersion lens, innumerable dark gray particles, just within the limits of microscopic visibility, are seen going through the typical Brownian movement against a light gray background. If a drop of the same ink is mixed with a drop of fresh blood, the carbon precipitates at once in the form of rather coarse black particles, assembling in small irregular clusters. I did not find this phenomenon mentioned in the papers of the other authors who used intravenous injections of India ink. This point is of outstanding importance, however, because it shows that after India ink enters the circulation, it ceases to be a "colloidal" carbon suspension, and turns into a common suspension of rather coarse carbon particles.

When the blood was examined under the microscope a few minutes after the intravenous injection of India ink, distinct black particles of carbon were seen floating among the blood corpuscles. They were of a size fairly easily visible even under medium power lenses and did not by far approach the limit of visibility. In many cases they were seen agglutinated and forming smaller or larger black clusters. This could easily be confirmed on sections, on which in the lumen of the blood vessels a similar picture was seen.

The fate of India ink injected intravenously has been followed by many investigators. Of the more recent workers, Wislocki [16] may be mentioned; in his paper an extensive bibliography on this subject can be found. According to Wislocki, India ink injected intravenously is deposited in the lumen of the blood sinuses or capillaries of the liver, the spleen, the bone marrow and the lung; one hour after the injection, phagocytosis of the coal particles is manifest; the active rôle in this process in the liver, the spleen and the bone marrow is played by the so-called "reticulo-endothelial" elements. In the lung, to which Wislocki paid special attention, one hour after the injection he found numerous interalveolar capillaries with tiny plugs of carbon in the lumen. Clasmatocyte-like cells, located in the partitions between the alveoli—their origin was not followed—begin to phagocytize the carbon. In this way a part of the originally solid mass of carbon is being converted into a mass of mononuclear cells loaded with granules of carbon. On the surface of the endothelial cells carbon granules also can be seen; later they may be found even in their cytoplasm. However, Wislocki emphasizes that these endothelial cells never show any sign of active phagocytosis. In the later stages, the India ink is carried by the phagocytes into the lymph channels and finally into the lymph nodes.

The relations of India ink, injected intravenously, to the cells of the vascular walls and especially to the endothelium are certainly by themselves of great interest. However, we repeated the experiments of Foot

16. Wislocki, G.: Am. J. Anat. **32**:423, 1924.

with the special purpose of solving the question of the origin of the mononuclear exudate cells, the polyblasts, in inflammation.

Regarding the first problem, the behavior of the endothelium toward the particles of carbon circulating in the blood, we obtained practically the same results, as McJunkin [9] and Foot [4] and, later, Wislocki.[16] The "endothelium," or better, the histiocytes, lining the sinusoids of the liver, the spleen and the bone marrow, accumulates large quantities of carbon particles immediately following the injection. In the vessels of the loose subcutaneous connective tissue of the abdominal wall—as well as probably in most of the other vascular regions of the body, except perhaps the central nervous system and the leptomeninges, in which the amount of carbon was always minimal—carbon particles were also easily found (Figs. 3 and 4). Their quantity was incomparably smaller than in the vessels of the spleen, the liver, etc.—the organs which Wislocki found to be the chief places of carbon deposits. Besides, the distribution of the carbon was uneven, and vessels with large quantities alternated with vessels which contained very little carbon or none. Nevertheless, in the earliest stages observed, capillaries with India ink can be found in many microscopic fields of a section. This is also the case in the immediate proximity of the foreign bodies; thus, the inflammatory reaction of carbon containing cells could easily be followed.

In some capillaries the clusters of precipitated carbon particles form emboli, sometimes apparently plugging and completely obstructing the lumen (Fig. 5 *Emb*). In the majority of the capillaries and capillary veins the endothelium in the earliest stages shows various quantities of unevenly sized carbon particles, single or in clusters, sticking to the free surface of the protoplasm. In slightly later stages, after six hours and more, the same black particles, some of them of large size, are seen partly embedded in the interior of the endothelial protoplasm (Figs. 3 and 4). If large particles are embedded in the endothelial protoplasm, the corresponding part of the cell may bulge distinctly into the lumen of the vessel (Fig. 3 *Ed'*). Thus, not only the histiocytes of the special organs mentioned above, but the endothelial cells of the common blood vessels also prove able to engulf fine particulate matter. The same has been observed recently in the vessels of the tongue of the living frog by F. Herzog [17] and Stilwell.[18] It is certain that this phenomenon is not due to active phagocytosis, and that it is not connected with ameboid movement and formation of pseudopodia. It is merely the result of the physical properties of the free surface of the endothelial protoplasm and is due to peculiar conditions of the surface tension of the latter.

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17. Herzog, F.: Ztschr. f. d. ges. exper. Med. **43**:79, 1924.
18. Stilwell, F.: Fol. häm. Arch., to be published.

The carbon particles circulating in the blood are taken up not only by the fixed histiocytes lining the sinusoids of the liver, spleen and bone marrow and by the common endothelium, lining the other vessels, but beginning with the earliest stages of the experiment, after from three to six hours, white blood corpuscles containing carbon particles are found everywhere in the circulation. This refers, first, to the polymorphonuclear special granular (pseudo-eosinophilic in the rabbit) leukocytes. On dry blood smears (Fig. 2 *Lkc*) and in the lumen of the blood vessels in sections (Fig. 1 *Lkc*) many of them are seen containing a few small carbon particles. Second, the majority of the monocytes (Figs. 2 and 3 *Mon*) also show carbon particles in their protoplasm. The particles here are often somewhat larger and more numerous than in the special granular leukocytes. Simpson [19] saw the number of monocytes increase in the blood of animals subjected to repeated intravenous injections of various kinds of colloidal substances and particulate matter. Although our experiments were of an acute character and although we did not make leukocyte counts in the blood, we also received the impression that in our animals the quantity of monocytes was larger than usual. However, it is known that of all the leukocytes the monocytes show a particularly uneven distribution in the vascular bed.

Finally, large free phagocytic cells were occasionally found in the lumen of blood vessels in sections (Fig. 3 *Hist'*). In blood smears they could not be found, probably because of their insignificant quantity. Their pale, vacuolated protoplasm contained large quantities of finer and coarser carbon granules, of which bulky, angular lumps occasionally obscured the nucleus. The latter seemed always to be very lightly stained and showed a wrinkled membrane.

These were the free histiocytes of Kiyono,[8] the "macrophages" of Simpson,[19] the hemohistiocytes of Ferrata.[20] In the blood of our animals the differences between these free histiocytes and the monocytes were usually distinct, and no transitional forms between them were seen, at least in the stages we observed.

It may be added that in many of our animals the blood after the injections of India ink contained a small quantity of special metamyelocytes. This may be looked on as the symptom of a slight irritation of the bone marrow.

CHANGES OF CONNECTIVE TISSUE SURROUNDING FOREIGN BODY

Earliest Stages (Three to Six Hours).—The tissue shows a slight edema, its texture is distinctly loosened and its elements are pushed

19. Simpson, M.: J. M. Res. **43**:77, 1922.
20. Ferrata, A.: Haematologica **2**:242, 1921.

apart. As a result of direct traumatic injury, a varying quantity of fixed cells in the immediate proximity of the foreign body—fibroblasts and histiocytes (resting wandering cells)—are seen undergoing necrosis; they contain disfigured, shrunken and darkly staining nuclei, whereas the protoplasm shows vacuolization and disintegration.

The vessels appear enlarged and tortuous, especially the venous capillaries. Their endothelium as yet does not show any distinct changes; its surface in many places is sprinkled with granules of India ink, as described above; in some cells the granules have already entered the protoplasm. The lumen shows an accumulation of leukocytes, special polymorphonuclear, as well as monocytes and lymphocytes. All, with the exception of the smallest lymphocytes, may contain particles of India ink.

The fibroblasts in the surrounding tissue as yet do not show any distinct changes. They are merely pushed apart from each other by the edematous liquid. The histiocytes (resting wandering cells) show the first signs of inflammatory reaction—they begin to contract and their protoplasm contains a varying quantity of clear vacuoles, which are especially numerous when egg yolk is injected into the tissue.

Special (pseudo-eosinophilic) granular leukocytes with polymorphous nuclei are present in the tissue. Their quantity rapidly increases; a part of them contain a few small carbon particles. They creep about in the tissue and are seen accumulating especially in the vicinity of the sponge; when yolk is injected, their distribution in the tissue is more diffuse. A varying quantity of these cells undergoes degeneration.

The origin of these leukocytes is obvious—they emigrate out of the blood vessels. However, typical pictures of their penetration through the endothelial vascular wall are not common in the fixed preparation. In the earliest stages now under consideration lymphoid cells are scarce in the tissue; pictures of their emigration out of the vessels are still more difficult to find than for the polymorphonuclear special leukocytes.

No signs of proliferation, mitotic or amitotic, can be found in any of the cells.

Medium Stages (Ten to Eighteen Hours).—Edema: The edema is extensive in these stages. The collagenous fibers appear partly torn and swollen, and are pushed widely apart by a liquid accumulated in the spaces between them; in some places scarce, delicate fibrin precipitates are seen. The degenerating cells, mentioned in the earlier stages, seem to be more numerous.

Blood Vessels: The blood vessels are seen in large quantities on the surface of the muscular aponeuroses. They all appear enlarged and have a tortuous course, especially the capillary veins. The endothelial cells are swollen; their oval, vesicular, clear nuclei bulge in many places

into the lumen; their protoplasm acquires a certain degree of basophilia. They show some rare mitotic figures; signs of amitotic division could never be found. The general distribution of particles of India ink on the whole remains the same as described previously; in some places the swollen endothelium shows a varying, sometimes large, amount of black particles (Fig. 4 *Ed*); in other places, the wall of the vessel is free from India ink. Only a few of the carbon particles seem to keep their original position on the inner surface of the endothelial cells; the intracellular position of the majority is certain. In exceptional cases an endothelial cell may contain, besides small particles, a large lump of carbon; the protoplasm is distinctly seen to cover this foreign body on the inner surface of the cell and to bulge into the lumen of the vessel (Fig. 3 *Ed'*). Here and there a capillary may be found with a lumen completely obstructed by a large carbon embolus (Fig. 5). In such cases the endothelial cells adjacent to the carbon mass always contain small black particles apparently detached from the embolus and taken up by the protoplasm.

Special attention was paid to the presumed loosening of the connection between the endothelial cells and their isolation and transformation into ameboid elements. The nature of the preparations was such that a phenomenon of this type could not possibly remain unnoticed. However, we failed to find anything suggesting such a possibility in the places in which the endothelium contained carbon as well as in the vessels completely free from India ink.

In the lumen of the dilated blood vessels—especially the capillary veins—a large accumulation of granulated and nongranulated white blood corpuscles is seen. In many places both types of leukocytes display a typical marginal position, and both, except the small lymphocytes, may contain a few small carbon particles in their protoplasm. In the monocytes this is especially often the case. The presence of carbon containing monocytes can be easily shown on dry smears of blood taken from the ear veins of the respective animals (Fig. 2 *Mon*).

Both lymphocytes and monocytes retained in the enlarged vessels show distinct signs of hypertrophy; this causes a gradual effacement of their differences. Transitional forms between lymphocytes and monocytes, ordinarily missing or rare in the circulating blood, seem to become common in the stagnant blood of the vessels described. The nucleus of the lymphocyte becomes larger, stains less dark and acquires a one-sided indentation and an excentric position. The protoplasm gradually accumulates on the indented side of the nucleus and may show ingestion of small particles of India ink.

In some cases exceptionally large free ameboid cells with a pale nucleus, a wrinkled membrane and a large amount of fine and coarse carbon particles, completely filling the protoplasm, can be found in the

lumen of the enlarged vessels (Fig. 3 *Hist'*). The cells are the free histiocytes of Aschoff [7] and Kiyono,[8] which, as mentioned in the foregoing, can be found in the general circulation on careful examination, and are known to originate in the sinusoids of the bone marrow, the liver, the spleen, etc.

As in the general circulation, in the enlarged vessels of the inflamed area, no distinct transition forms between them and the true monocytes can be found.

All the described white blood cells and the free histiocytes often can be found closely adjacent to the inner surface of the endothelium in the dilated blood vessels (Fig. 3). No difficulty was encountered in distinguishing them from the carbon containing or empty endothelial cells.

PENETRATION OF PARTICLES OF INDIA INK THROUGH WALLS OF VESSELS

During the stages now under consideration, an important phenomenon can be noticed. The carbon particles contained, as has been described, in the protoplasm of the endothelial cells of the capillaries, are seen passing through the unchanged, intact endothelium into the tissue surrounding the vessels. Some of them, leaving the protoplasm of the endothelium on its outer surface, seem to lie freely between the cells and the thin collagenous fibers (Fig. 8 *II*). Most of them, however, are transferred from the protoplasm of the endothelium directly into the protoplasm of cells intimately adjacent to the outer surface of the capillaries (Figs. 4 to 6 *Per*).

These elements contain an elongated or oval nucleus, almost similar in its inner structure to the endothelial nuclei; their protoplasm is pale and not distinctly defined; in the majority of the cases it is stretched parallel to the axis of the capillary, thus displaying a spindle-shaped form on longitudinal sections of the latter. In the subcutaneous tissue—with the technic used in this investigation—these cells rarely show distinct transverse processes encircling the capillary.

It is obvious that these elements are the adventitial cells of the capillaries or the pericytes of Zimmermann [21]—a cell type which recently has received much attention and which by some investigators is made responsible for the contractility of the capillaries. The recent experiments of Stilwell,[18] who repeated the work of F. Herzog [17] on the blood vessels of the living tongue of the frog after intravenous injection of India ink, did not give convincing evidence of the contractility of these elements. They have shown instead that the pericytes actively collect particles of India ink, which, after having been engulfed by the endothelial protoplasm, leave the latter on its outer surface.

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21. Zimmermann, K.: Ztschr. f. Anat. u. Entwgesch. **68**:29, 1923.

The same is true for the pericytes of the capillaries in the inflamed subcutaneous connective tissue of the rabbit. It is possible, of course, that the same phenomenon—the transportation of particulate matter from the endothelium into the pericytes—might also be observed, perhaps on a smaller scale, in the absence of inflammation. Our special aim was, however, to elucidate the changes of the endothelium under the influence of the inflammatory stimulus, and the migration of the particles of India ink under the conditions of our experiments manifested itself with a peculiar clearness.

Whether pericytes and the endothelial cells are connected with each other by means of protoplasmic processes and the carbon particles flow through the protoplasm of these connections from one cell to another, or whether they are simply eliminated from the endothelial cell on its outer surface and then immediately enter the protoplasm of the pericytes, cannot be decided. The occasional presence of seemingly free carbon particles outside the endothelium suggests the second explanation. On the other hand, in many cases an apparently uninterrupted row of black particles seems to connect the endothelial cell with a pericyte.

The thin protoplasmic layer of a pericyte adjacent to the endothelium may contain single, tiny carbon particles, arranged longitudinally one behind the other. Often the endothelium also contains similarly arranged particles, and in such a case the wall of the vessel is lined by two parallel rows of black granules. Sometimes the black granules in the protoplasm of the pericyte are numerous and may form an angular irregular cluster, partly or completely concealing the nucleus.

We were trying to find evidence of the possible migration or recession of the carbon containing endothelial cells into the surrounding tissue, but in this we were unsuccessful. The mitoses of the endothelium are rare and cannot explain the appearance of numerous carbon containing cells paralleling the vascular wall. The endothelial tube everywhere remains intact and continuous.

EMIGRATION OF LEUKOCYTES

The classical pictures of emigration of leukocytes with distinctly constricted nuclei from the blood vessels into the tissue are present but are by no means numerous (Fig. 1 *x*). This fact, which seems to be in striking contradiction to the large quantity of leukocytes found in the tissue, has been discussed by Maximow in several of his papers. He has also pointed out that this scarcity of the emigration pictures of nongranular leukocytes, which has been looked on as one of the strong proofs against the hematogenous origin of the polyblasts, pertains equally to the special granulated leukocytes whose hematogenous origin cannot be doubted. The explanation can be sought, on the one hand, in the

rapidity of the process, and, on the other hand, in the peculiar position of the emigrating cells when they pass through the endothelial wall. In most cases the leukocytes traverse the wall of the capillary in a decidedly oblique or even parallel direction, sometimes causing a distinct splitting of the endothelial protoplasm into two layers and undergoing for a while a considerable compression (Fig. 3 *x*). Such pictures of emigration can easily be overlooked. This pertains to the special granular (pseudo-eosinophilic) leukocytes with the polymorphous nucleus and to the non-granulated leukocytes—the lymphocytes and monocytes as well. Many of the emigrating special granular leukocytes and monocytes contain small granules of India ink in their protoplasm (Fig. 3 *x*).

The hypertrophy of the emigrating lymphocytes and monocytes, which began, as we have seen, while the cells were still in the lumen, continues after their migration into the tissue; in this way the emigrated nongranulated blood leukocytes transform themselves into polyblasts (Figs. 1 and 4 *Plb'*).

FIBROBLASTS

The fibroblasts in the edematous tissue are scattered at considerable distances from each other (Figs. 1 and 4 *Fbl*). They keep their general structure, and the outlines of their long, wing-shaped or spear-shaped processes are particularly well distinguishable in the tissue spaces filled with clear liquid. In many places, especially in the proximity of the foreign body, their protoplasm appears swollen and hypertrophied, and assumes a distinct basophilic staining property; it also often contains a variable number of vacuoles. The nucleus remains unchanged in its typical inner structure and always enables one to identify the cell. Rounding off, formation of ameboid pseudopodia and transformation into wandering cells could never be detected. Mitoses begin to appear in many fibroblasts. Carbon particles seem to enter their protoplasm only rarely and in small quantities.

HISTIOCYTES OR RESTING WANDERING CELLS (CLASMATOCYTES)

The histiocytes of the loose subcutaneous tissue near the foreign body are mobilized (Fig. 5 *Hist*). For the most part, they keep their former position, but appear enlarged. They are rounding off and display ameboid pseudopodia of varying form and size. Their protoplasm has a distinct reticular structure and contains—especially in the experiments with the introduction of egg yolk into the subcutaneous tissue—numerous clear vacuoles and granular inclusions. Their phagocytic activity is clearly manifested by the presence of normal or degenerating special granular leukocytes in their protoplasm. Occasional small particles of India ink can be found in some of the histiocytes which are closely adjacent to the capillaries. The nucleus of these cells keeps its char-

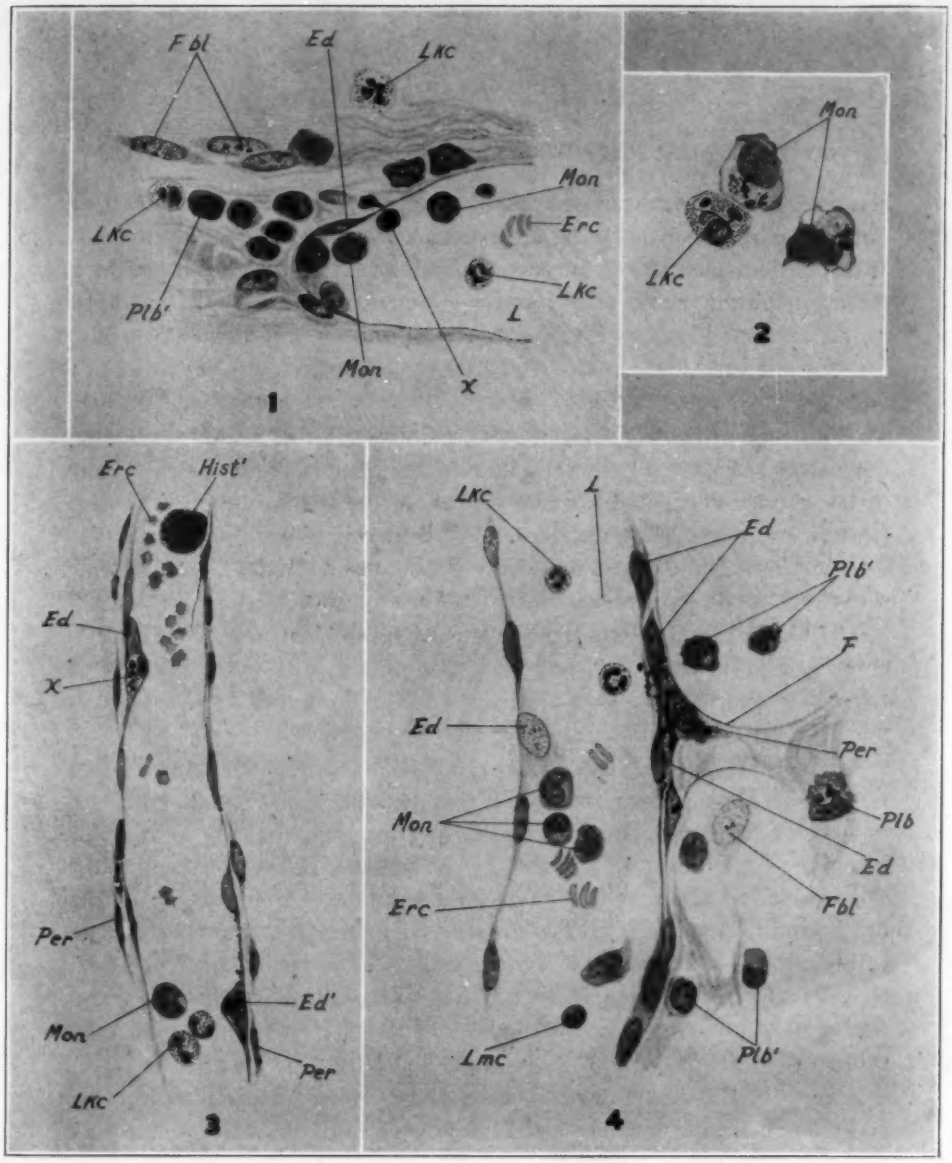

Fig. 1.—Series *a*, fourteen hours: connective tissue surrounding the foreign body; *x*, emigration of a lymphocyte; a special leukocyte in the lumen of the vessel (*Lkc*) and one of the extravascular polyblasts (*Plb'*) of hematogenous origin contain carbon; × 1100.

Fig. 2.—Series *b*, ten hours: dry smear of blood from the ear vein. Two monocytes (*Mon*) and a polymorphonuclear special leukocyte (*Lkc*) containing carbon granules; + 1100.

Fig. 3.—Series *b*, seven hours: blood vessel near the area injected with egg yolk; *Ed'*, endothelial cell with a large lump of carbon; *x*, emigration of special leukocyte; *Mon*, monocyte containing carbon particles; × 1100.

Fig. 4.—Series *a*, fourteen hours: connective tissue surrounding the foreign body. Capillary vein with endothelium (*Ed*) and pericytes (*Per*), partly containing granules of India ink; *Plb*, polyblast with carbon; one of the monocytes (*Mon*) in the lumen of the vessel contains carbon; × 1100.

In this illustration and in those that follow, *Ed* indicates endothelium; *Emb*, carbon emboli; *Erc*, erythrocytes; *F*, fat cells; *Fbl*, fibroblasts; *Hist*, histiocytes (resting wandering cells); *Hist'*, free intravascular histiocytes containing carbon; *H*, free granules of India ink; *L*, lumen of blood vessel; *Lkc*, special polymorphonuclear leukocytes; *Lmc*, lymphocytes; *Mon*, monocytes; *Per*, pericytes; *Per'*, pericytes containing carbon and receding from the wall of the vessel; *Plb*, polyblasts; *Plb'* polyblasts of hematogenous origin.

acteristic features and can be easily distinguished from the nucleus of the fibroblasts by its smaller size, its irregular outlines and the darker stain. In somewhat later stages one can follow the gradual transformation of these mobilized histiocytes into large ameboid phagocytic cells, the histogenous polyblasts (Fig. 4 *Plb*).

SPECIAL GRANULAR POLYMORPHONUCLEAR LEUKOCYTES

This type of cell is found in large quantities in the tissue surrounding the foreign body. These cells accumulate markedly in the proximity of the sponge and penetrate into its cavities, resorbing the agar. Huge masses of them are scattered also between the adjacent striated muscle fibers. Many of them contain granules of India ink, and many show various stages of degeneration and disintegration.

It is needless to discuss the origin of these elements—they have all emigrated from the blood vessels, although, as we have stressed in the foregoing, the pictures of their emigration are not much more common than for the nongranulated leukocytes.

Lymphoid, nongranulated wandering cells (with round compact, nonpolymorphous nucleus), polyblasts or mononuclear exudate cells, are now also numerous in the inflamed tissue, and their number continues to increase (Figs. 1 and 4 *Plb, Plb'*). The stages now under consideration are especially important for the decisive solution of the problem of their origin and histogenesis. It is distinctly characteristic of the early stages of inflammation that the polyblasts, infiltrating the tissue, are represented by cells of different size and structure, so that two extreme types connected by an uninterrupted series of transitional forms are easily demonstrable (Fig. 4 *Plb'*).

Many of the round ameboid cells are morphologically identical with common small and medium sized lymphocytes, as described in the foregoing for the blood, filling the enlarged capillaries and capillary veins. The only difference detected is the distinct ameboism of the cells in the tissue, while most of the intravascular specimens are spherical.

The other extreme is represented by cells of the size of blood monocytes or slightly larger. However, even the largest among them does not as yet reach the size of the local histiocytes. They have an abundant, slightly basophilic protoplasm, accumulated on one side of the excentrically located, usually slightly folded and indented, nucleus; the quantity of chromatin is smaller than in the nucleus of the lymphocytes, and the nucleus therefore stains lighter than in the latter. Sometimes a distinct cytocentrum is seen at the indented surface of the nucleus. The protoplasm, whose ameboid character is more manifest than in the small cells, frequently contains a few small carbon granules and clear vacuoles. The largest cells may also contain débris of degenerated special leukocytes.

Between the two extremes described every possible transition can easily be found at any place in the tissue.

Mitoses in the polyblasts are extremely rare. The distribution of the polyblasts in the edematous tissue is irregular. They are scattered in small groups or singly everywhere around the enlarged blood vessels in the vicinity of the sponge. Some of them are seen, together with the leukocytes, penetrating into the cavities of the foreign body.

According to Foot,[4] in the stages under consideration we should expect to find the transformation of the endothelial cells of the blood capillaries into polyblasts in full swing. However, our preparations failed to furnish us any facts supporting this assumption.

The endothelial cells, as I have already mentioned, show a distinct swelling (Fig. 4 *Ed*), and during these stages just begin to enter the period of active mitotic proliferation. But no trace of loosening of the endothelial membrane into single cells and of their isolation and rounding off as free ameboid elements and of their movement into the tissue could be found. There was, moreover, no bulging of these cells into the lumen of the vessel which could be supposed to result in the production of free intravascular cells in the form of the so-called "endothelial leukocytes."

As we have pointed out in the foregoing, the hypertrophying lymphoid cells in the enlarged capillaries and capillary veins, i. e., the lymphocytes and monocytes, on one hand, and the polyblasts, the "mononuclear exudate cells" outside the vessels, in the tissue, on the other hand, are morphologically similar in every respect (Figs. 1 and 4). The only difference is the further advancement of a part of the extravascular cells in their progressive development and enlargement. Cells from either group may contain a variable number of carbon particles. Pictures of emigration of similar cells can be demonstrated, as also has been stated. The only possible conclusion, therefore, seems to be that the ameboid mononuclear exudate cells rapidly accumulating in these early stages in the tissue are emigrated nongranular blood leukocytes, lymphocytes and monocytes.

It is important, from the general hematologic point of view, that during this process of emigration and transformation no sharp line of distinction can be drawn between the lymphocytes and monocytes. Both cell types, intravascularly as well as extravascularly, are connected by a continuous series of gradual transitions. Both take indiscriminately an active part in the production of hematogenous polyblasts.

Later Stages (Twenty-Four to Forty-Eight to Seventy-One Hours).—Of the phenomena shown by the tissue surrounding the foreign body in these stages, only the facts concerning the polyblasts need a more detailed discussion.

The edema still persists partly, but the cellular elements of the tissue, due to their continued increase in number, appear arranged much closer to each other. The tissue is overflowed with special granular leukocytes; they accumulate in increasing quantities in the sponge and there undergo degeneration. The fibroblasts all show distinct hypertrophy, an increase of the basophilia of their protoplasm, and are found everywhere in active mitotic proliferation. As in the earlier stages, they do not become transformed into ameboid exudate cells.

The vessels are still enlarged; their endothelium is considerably swollen and occasionally contains mitotic figures. Here again the most attentive search fails to show any signs of their supposed transformation into free ameboid cells either in the lumen or on the outer surface of the wall of the vessel.

Many of the endothelial cells still contain a varying quantity of carbon particles. But in the cells, surrounding the capillaries and adjacent to their endothelium—the pericytes, described in the foregoing, and the histiocytes (resting wandering cells), with occasional transitions between the two—the carbon particles are found in larger numbers than in the preceding stage.

These perivascular cells are seen to recede from the immediate vicinity of the capillaries farther into the tissue carrying the carbon particles with them (Fig. 4 *Per*). It is possible that the carbon may also be transmitted from cell to cell without an actual changing of the position of the cells themselves.

Sometimes small vessels, capillary veins, are found, whose endothelium, as the result of mitotic proliferation, becomes double layered. It is possible to assume that in such cases the outer layer of endothelial cells recedes into the tissue, acquiring the properties of fibroblasts, as has been shown by Maximow [2] in his early papers on inflammation. There are no indications of a transformation of such receding endothelial cells into ameboid elements. They are to be differentiated from the pericytes. This process may well be compared with the active participation of endothelium in the production of fibroblasts during the organization of an intravascular thrombus.

The emigration of the special leukocytes continues for a while, and our experiments gave us the impression that the presence of lecithin in the foreign body stimulates this process and increases the number of the emigrating cells. The carbon particles in the newly migrated cells are becoming more and more scarce.

The quantity of the ameboid mononuclear exudate cells in the tissue during the present stages reaches its climax. In many places they nearly crowd out the other cell types. Emigration of lymphocytes and monocytes is still going on. An important change has taken place.

Whereas in the preceding stages there was a distinct gap between the local, large, mobilizing histiocytes (resting wandering cells) and the smaller, round (lymphocyte-like and monocyte-like) polyblasts of hematogenous origin, now the local histiocytes seem to have disappeared almost completely and the tissue contains, instead, great quantities of large ameboid, phagocytic cells, among which no distinction can be made as to their local or hematogenous origin. There can be only one explanation of this fact. The local histiocytes have all been mobilized and are all transformed into large polyblasts or macrophages; but the latter are so numerous and show such convincing transitional forms to the smaller lymphoid exudate cells that there cannot be any doubt as to the origin of a considerable part of the largest polyblasts from the hematogenous nongranulated leukocytes, which in the former stage were small and could be differentiated sharply, from the awakening histiocytes which in the meantime have developed progressively.

The large polyblasts or macrophages need not be described in detail. Their excentrically located, usually kidney-shaped nucleus, which is always darker than in the fibroblasts, is a secure criterion for their identification. Mitoses can be found occasionally, but are rare. The protoplasm is sometimes vacuolated. Engulfed and partly digested special granulocytes are common. If their granules scatter in the protoplasm of the phagocytic polyblast, such cells can easily be mistaken for myelocytes. Some of the polyblasts contain carbon granules (Fig. 4 *Plb*). In the experiments with the agar sponges, the method of Ciaccio [22] in the majority of the polyblasts reveals the presence of "lecithin" granules. In the experiments with egg yolk they contain yolk granules and numerous vacuoles.

In places in which lumps of agar have been pressed out of the sponge and lie freely in the tissue, the polyblasts assemble in large groups, surround the agar and fuse together, forming multinucleated giant cells.

As the emigration of new lymphocytes and monocytes still continues, the tissue always contains transition forms from the largest polyblasts of the macrophage type to the smallest, lymphocyte-like polyblasts, which have just left the blood vessels.

On the contrary, transition forms between endothelial cells and polyblasts, which could be made responsible for the endothelial origin of at least a part of the latter, are never found.

OMENTUM

The tissue of the omentum of our animals that received intravenous injections with India ink and intraperitoneal injections with a small

22. Ciaccio, C.: Anat. Anz. **35**:17, 1910.

amount of silver nitrate, proved to be especially favorable for the study of the transformations of the endothelial cells of the small blood vessels. The capillaries in the rabbit's omentum are extremely long tubes, branching slightly and only in special places, as for instance in the vascular milky spots. They show a distinct so-called adventitia capillaris, a thin collagenous membrane, surrounding the endothelial tube. With this membrane are connected numerous pericytes—elongated spindle-shaped cells, whose nuclei and thin cell bodies everywhere are seen, with the adventitia capillaries closely adjacent to the outer surface of the endothelium (Figs. 7, 9 and 10 *Per*). Often transversely arranged processes of these cells are seen encircling a smaller or larger part of the periphery of the capillary.

These pericytes, especially in the omentum, seem to play an important rôle in the production of new cells and in the reactions of the tissue toward irritations of various kinds. Marchand,[23] who previously in his papers dealing with the inflammatory changes of the omentum described only one type of "adventitial cells" or "clasmatocytes" near the capillaries, elements which are now known to belong to the phagocytic and dye-storing cell type of the histiocytes, at the present time,[11] under the influence of the investigations of his student Herzog,[24] distinguishes two cell types accompanying the capillaries. This view is now also adopted by Maximow.[25] The one type of cell seen best in animals intravitally stained with lithium carmine or trypan blue is the common histiocytes or clasmatocyte (Figs. 9 and 10 *Hist*). These cells react in inflammation by rounding off and transforming themselves into large ameboid, phagocytic, wandering cells, the polyblasts of Maximow. The others are the cells intimately adjacent to the endothelium of the capillaries (Figs. 7, 9 and 10 *Per*). They do not store vital dyes and, in the structure of their nucleus and the behavior of their protoplasm, resemble mesenchymal cells. They are elements of embryonic type, keeping the various potencies of development which are characteristic of the mesenchymal cells of the embryo. They can give rise—provided there is adequate stimulus—to various other types of cells, and may become differentiated in several ways. The two most common results of their differentiation are, on the one hand, the phagocytic and dye-storing histiocytes (resting wandering cells, clasmatocytes) and, on the other hand, common fibroblasts. In inflammation they are usually seen to move away from the vessel (Fig. 8 *Per*, Fig. 10 *Per*) and to become transformed into

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23. Marchand, F.: Verhandl. d. Deutsch. path. Gesellsch. **4**:124, 1901.

24. Herzog, G.: Beitr. z. path. Anat. u. z. allg. Path. **61**:377, 1916.

25. Maximow, A.: "Bindegewebe und blutbildende Gewebe," in von Möllendorff, W.: "Handbuch der mikroskopischen Anatome," Berlin, J. Springer, to be published.

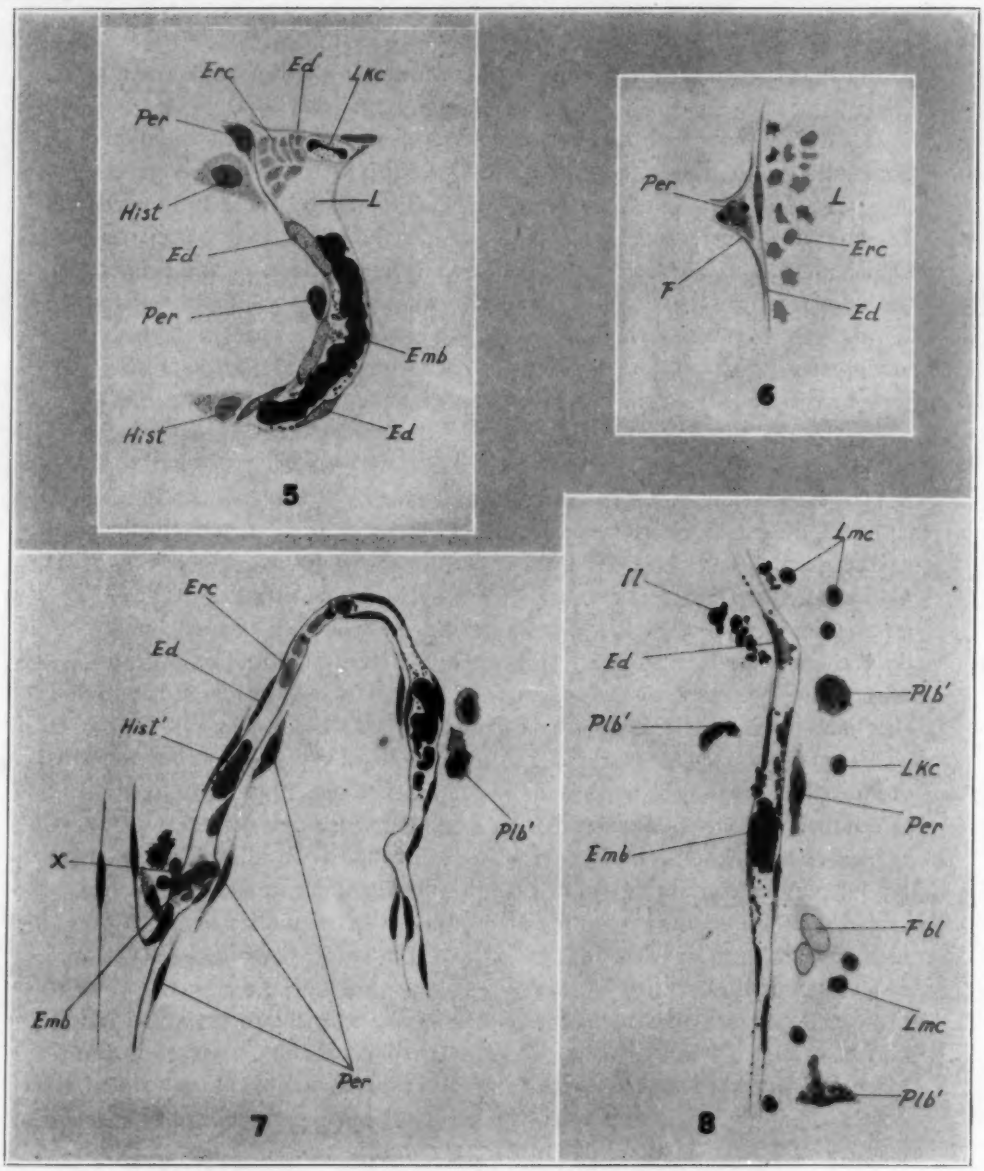

Fig. 5.—Same slide as in figure 3. Capillary with carbon embolus (*Emb*) in the lumen (*L*); × 1100.

Fig. 6.—Series *b*, fifteen hours: part of the wall of a capillary vein in fat tissue, adjacent to the area of yolk injection; *Per*, pericyte containing carbon; × 1100.

Fig. 7.—Series *b*, ten hours: omentum; capillary loop with carbon emboli (*Emb*), and carbon containing histiocytes in the lumen; endothelium (*Ed*) unchanged; *x*, emigration of a carbon containing special leukocyte; × 1100.

Fig. 8.—Series *b*, fifteen hours: omentum; capillary with carbon embolus (*Emb*) and endothelium (*Ed*) containing granules of India ink but otherwise unchanged; × 1100.

histiocytes, which at once, under the influence of the inflammatory stimulation, develop further into ameboid polyblasts.

In the animals that received intravenous injections with India ink, the capillaries of the omentum showed carbon particles in many places. The stages of ten to fifteen hours proved to be the most interesting. The microscopic study is highly facilitated by the possibility of preparing whole mounts of the fixed and stained transparent membrane without the necessity of recurring to the section method. This implies another advantage—the capillaries are seen with all their parts intact and arranged in the plane of the microscopic stage, whereas in the sections they are often cut off at the most important place, so that one has to resort to the difficult and not always satisfactory comparison of the serial sections.

In the capillaries of the omentum, besides the usual sprinkling of the endothelial surface with smaller or larger, isolated or clustered carbon particles (Figs. 8-10 *Ed*), emboli in the form of large lumps of agglutinated carbon particles are especially common (Figs. 7-10 *Emb*). They plug and obstruct the lumen, sometimes causing a distinct bulging on the outer surface of the thin endothelial membrane. The proximal part of the obstructed capillary in such cases is usually enlarged, while the distal part sometimes appears collapsed.

In many places large carbon filled free histiocytes, occurring more frequently than in the vessels of the subcutaneous tissue, are seen in the lumen of the capillaries, either together with the free lumps of carbon or as isolated cells (Fig. 7 *Hist'*). Monocytes and special granular leukocytes containing small carbon particles and small lymphocytes can also be found in the capillaries, although their number here, on the contrary, is smaller than in the enlarged tortuous capillaries of the subcutaneous tissue (Fig. 10 *Mon*). In the omentum the emigration of these cells can also be seen, sometimes in the immediate proximity of carbon emboli (Fig. 7 *x*). However, this phenomenon, at least in the stages mentioned, is not as prominent as in the subcutaneous tissue; and, correspondingly, the majority of the polyblasts in the tissue are of local origin—mobilized histiocytes (resting wandering cells or clasmatocytes. Figs. 9 and 10 *Plb*).

In the manner described for the subcutaneous tissue, the small carbon particles, first sticking to the inner surface of the endothelium, enter its protoplasm. After from ten to fifteen hours, many of them have passed through the thin endothelial membrane and have found their way into the protoplasm of the adjacent pericytes (Figs. 8-10 *Per*). This is especially manifest and is being conducted on a large scale where the large carbon emboli are located; in all probability at these points the vitality of the endothelium is reduced and the permeability of its

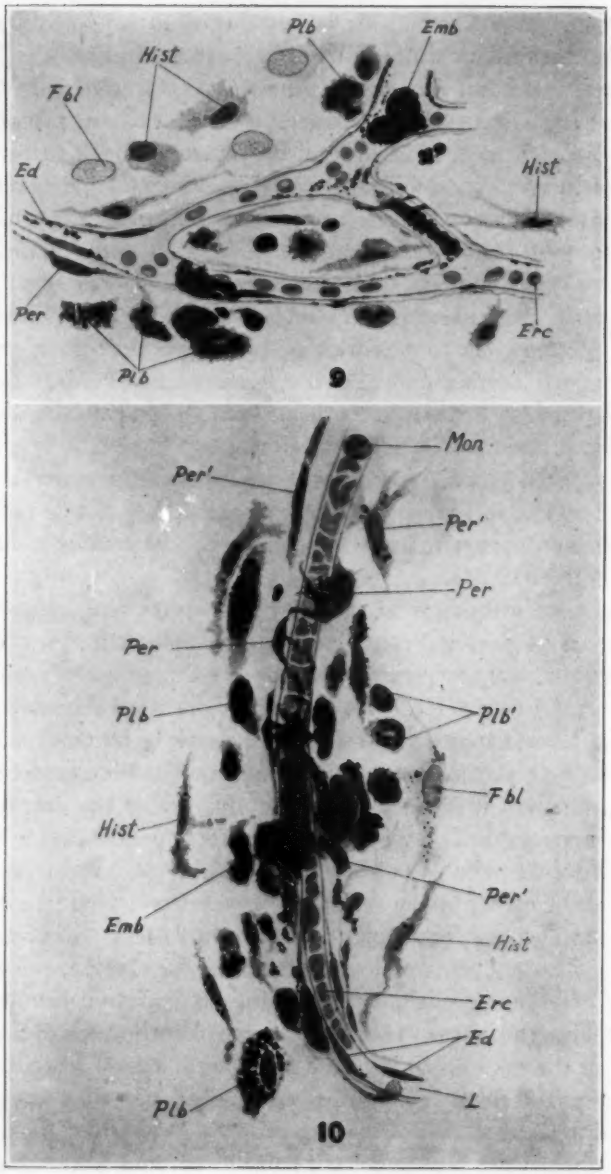

Fig. 9.—Series *b*, fifteen hours: omentum; capillaries with carbon emboli and endothelium (*Ed*), containing granules of India ink; the capillary wall is paralleled by a distinct adventitia capillaris with pericytes (*Per*) also containing carbon; × 1100.

Fig. 10.—Same slide as in figure 9. Capillary with carbon embolus (*Emb*) surrounded by numerous pericytes (*Per, Per'*) containing carbon and receding from the endothelial tube; the perivascular histiocytes (*Hist*) also contain carbon; × 1100.

protoplasm increased. In such places the cells surrounding the plugged section of the capillary are engorged with carbon particles (Fig. 10); some of the latter may even be found freely scattered in the tissue (Fig. 10 *II*). The pericytes, crowded full of carbon, probably under the influence of this stimulus, round off and transform themselves into large ameboid polyblasts (Fig. 10 *Plb*), moving away from the vessel into the tissue. Many of them, however, may keep their position on the outer surface of the endothelium, or, if they also move away, partly keep their connection with the outer surface of the capillary (Fig. 10 *Per'*). But in this case the rounding off of the cell is delayed, and it first assumes the character of a fixed histiocyte with dark protoplasm, a sharp, rugged outline and a darker, irregular nucleus. Later these histiocytes can also become transformed into round ameboid polyblasts (Fig. 10 *Plb*).

The fibroblasts—which in the serous membranes generally seem to be less differentiated than in the common loose connective tissue of the subcutis—near the capillaries may sometimes also contain a few carbon granules (Fig. 10 *Fbl*).

The number of emigrated granular leukocytes and of polyblasts of hematogenous origin, emigrated lymphocytes and monocytes, containing or not containing carbon particles, in the stages now under consideration, is smaller in the tissue of the omentum than in the subcutaneous tissue.

The most important observation on the mildly irritated omentum in animals that received injections with India ink is the complete passivity of the endothelium in the process of production of the ameboid mononuclear phagocytic cells, the polyblasts. The endothelial wall of the capillaries, even in the embolized sections, always remains continuous; its cells do not change their position; they never transform themselves into ameboid elements and never produce polyblasts. There is also no production of "endothelial leukocytes" in the lumen. The carbon particles enter the endothelial protoplasm, pass through it and thus find their way into the tissue, where they are, for the most part, at once taken up by the pericytes. These cells in their turn may either remain unchanged and keep their place, or, especially when they have engulfed large quantities of carbon, they may move away into the tissue and transform themselves into either common histiocytes (resting wandering cells, clasmatocytes) and then into polyblasts or directly into round, ameboid polyblasts.

CONCLUSIONS

In confirmation of the previous findings of Maximow,[2] the polyblasts, the mononuclear exudate cells in the inflamed tissue, arise partly through mobilization of the local histiocytes, the resting wandering cells of the loose connective tissue, and partly through rapid hypertrophy of the

emigrated lymphocytes and monocytes. The hematogenous cells, which in the earliest stages of inflammation are much smaller than the polyblasts of local histiocytic origin, quickly become indistinguishable from the latter and join them in their further transformations. It may be pointed out in connection with these findings that Maximow [26] has recently succeeded in obtaining results with the method of tissue culture which strongly corroborate the concepts of the origin of the polyblasts as outlined in the present paper. If leukocytes of the blood of an adult rabbit are cultivated outside the body in a suitable nutritive medium, the lymphocytes as well as the monocytes in the course of a relatively short time are seen to develop into large, ameboid, phagocytic, carmine-storing polyblasts of the macrophage type; these cells also show a considerable capacity for mitotic proliferation.

M. Lewis [27] came to similar conclusions while incubating drops of blood of various animals in a moist chamber. However, she draws a sharp line of distinction between the monocytes and lymphocytes, and believes only the former to be capable of hypertrophy and macrophage formation.

That the lymphocytes and monocytes, on one hand, and the resting wandering cells or histiocytes, on the other hand, are closely related cell types, has been shown by the embryologic researches of Maximow [28] and confirmed recently by Alfejew.[29] Therefore, the double origin of the polyblasts both from local and hematogenous elements seems natural.

The endothelium of blood vessels in tissue cultures, as Maximow [26] has shown, does not give rise to ameboid elements. Long slender fusiform cells grow out of the severed ends of small arteries and gradually become transformed into strands of typical fibroblasts.

In our experiments, performed by the method of intravenous injections of India ink according to McJunkin and Foot, we failed to find any proof for the presumed active participation of the endothelium of blood vessels in the formation of polyblasts. The particles of India ink, after having entered the endothelium, pass through its protoplasm and are taken up by cells, surrounding the endothelial tube—the pericytes.

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26. Maximow, A.: Klin. Wchnschr. **4**:1486, 1925.
27. Lewis, M.: Am. J. Path. **1**:91, 1925.
28. Maximow, A.: Arch. f. mikr. Anat. **73**:444, 1909; Fol. häm. **4**:611, 1907.
29. Alfejew, S.: Fol. häm. Arch. **30**:111, 1924.

SO-CALLED ACRODYNIA OR ERYTHREDEMA (SWIFT'S DISEASE)

A PATHOLOGIC STUDY OF TWO NECROPSY CASES *

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Since Swift in 1914, under the clinical designation of erythredema, reported at the Australasian Medical Congress fourteen cases presenting a similar clinical picture of red hands and feet occurring in infants and young children, about 230 cases of this syndrome have been reported in the literature. At the Brisbane Conference in 1920, Wood said that he and Hobill-Cole of Melbourne had collected 91 cases, and other reports since that time bring the total number reported from Australia and New Zealand up to about 120. The first report in America was that made by Weston in 1920; he described under the designation acrodynia eight cases of the same condition seen by Australasian observers. At the meeting of the Swiss Pediatric Society held in Berne, in 1922, Feer reported observations on cases showing the same classical syndrome, under the designation of a "Neurosis of the Vegetative Nervous system in Young Children." His was the first European published observation. Since 1922 reported cases have rapidly multiplied, especially in America, where a hundred or more have been reported. Other cases have been reported in Switzerland, England, Scotland, Holland and Sweden. The literature of the present year has been especially prolific in articles bearing on this subject; and the papers of Bilderback,[1] Butler,[2] Foerster,[3] Rodda,[4] and Jenny [5] may be consulted for full clinical descriptions and bibliography of this condition.

Briefly, the clinical syndrome consists of three groups of symptoms: nutritional, nervous and cutaneous, occurring in infancy and early childhood, such as loss of weight and appetite, weakness, extreme irritability, sleeplessness, paresthesias, loss of reflexes, photophobia, paresis, erythema, swelling, cyanosis, coldness of hands and feet, high blood pressure, excessive perspiration, miliaria, desquamation, loss of hair and teeth. The affected child may present a dramatic clinical picture of

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* From the Pathological Laboratory, University of Michigan.

1. Bilderback, J. B.: Acrodynia, J. A. M. A. **84**:495 (Feb. 14) 1925.
2. Butler, J.: Erythredema, Arch. Dermat. & Syph. **11**:166 (Feb.) 1925.
3. Foerster, H. R.: Erythredema Polyneuritis, Arch. Dermat. & Syph. **12**:17 (July) 1925.
4. Rodda, F. C.: Acrodynia, Am. J. Dis. Child. **30**:224 (Aug.) 1925.
5. Jenny: Schweiz. med. Wchnschr., July, 1925.

pink hands and feet, knee-chest position with head buried in the pillow, chewing of fingers or wringing the hands and almost constant movement or whining. The great majority of the patients recover after several months; some after one or two years. The deaths have been due to intercurrent or terminal infections, chiefly bronchopneumonia. Forced feeding alone apparently will bring about a cure; other patients have shown rapid improvement after the removal of tonsils and adenoids.

As to etiology, nothing is known. It has been regarded as a post-influenzal sequela, as an avitaminous or deficiency disease resembling pellagra, as a chronic respiratory infection or an intoxication arising from infections of the upper respiratory tract, or as a toxic neurosis of the vegetative nervous system. The question of a specific infection of unknown nature has also been broached, but no proof exists in support of this theory. In the cases developing after a previous infection there was a definite period of one to several months before the development of the picture of acrodynia. These previous infections have been almost wholly respiratory tract infections, although in several cases diarrhea has occurred before the onset of the symptoms of hyperirritability. As to the food deficiency theory, the majority of the patients were on a proper diet. No relation to syphilis has been found. The cerebrospinal fluid shows no striking changes. No relationship to the French epidemic of "acrodynia" in 1828 has been shown.

The various theories as to the nature of this disease are reflected in the various terms applied to it, such as: dermatopolyneuritis, erythredema polyneuritis, epidemic erythema, epidemic erythredema, polyneuritis, pellagra-like polyneuritis, toxic erythredema, toxic neurosis, etc. The terms erythredema, pink disease, acrodynia, etc., apply to the prominent clinical features of the disease. All of these designations are unfortunate and misleading.

As to the pathology of the condition, still less is known. The mortality, so far as the cases reported go, has been slight, and there have been but few necropsies, and no thoroughly studied necropsy case. Skin biopsies have been made in a few cases, and the microscopic changes reported. In the ninety-one cases collected by Wood, there were only five deaths, four from bronchopneumonia and one from heart failure. As to the presence of any specific pathologic changes, in their fatal cases, the Australian observers report only negative necropsy findings. Byfield [6] reported necropsy findings, in one of his cases, of gliosis about the central canal of the spinal cord, with poor staining of the anterior horn cells proximal to the anterior commissure; the dorsal columns were normal. In the sciatic nerve there were edema and swell-

6. Byfield, A. H.: A Polyneuritic Syndrome Resembling Pellagra-Acrodynia. Seen in Very Young Children, Am. J. Dis. Child. **20**:347 (Nov.) 1920.

ing of the myelin sheaths, and edema of the perineurium and epineurium without cellular infiltration. The posterior roots of the lumbar cord also showed edema and swelling of the myelin sheaths in the fibers of the root and in that portion of the nerve lying between the ganglion and spinal cord. He interpreted the findings as being of the nature of a post-influenzal radiculitis or a sensory polyneuritis. He suggests also the possibility of an infective trophoneurosis. He saw four deaths in seventeen cases, one from deep phlegmon, one from miliary tuberculosis, the other two from inanition and pneumonia.

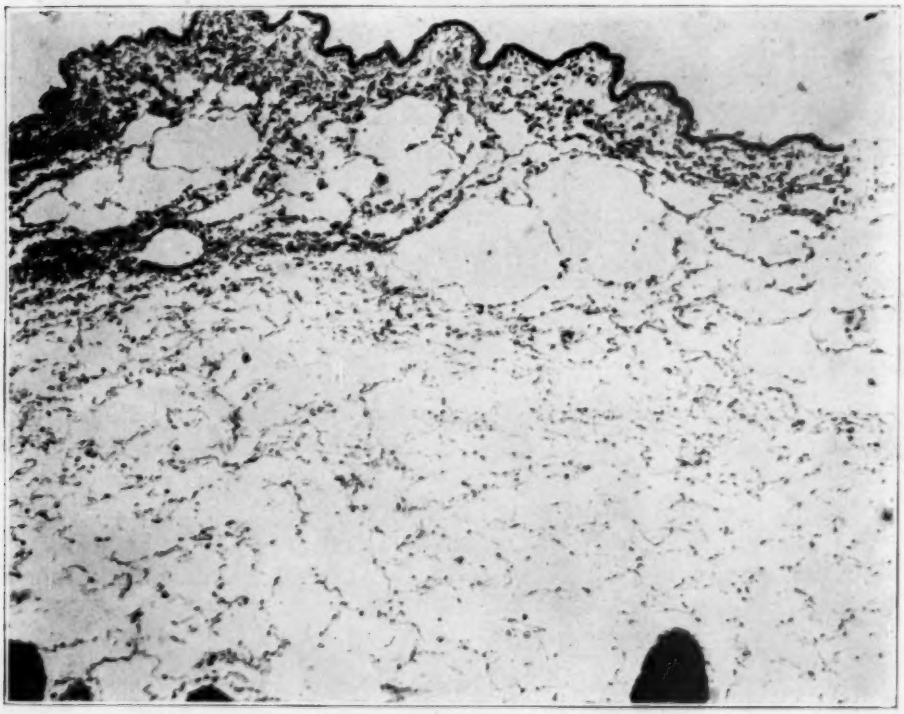

Fig. 1 (Case 1).—Section of edematous meninges from the brain. Extreme edema and increase of reticulo-endothelial cells.

Paterson and Greenfield [7] reported the findings in two necropsy cases. They found destruction of the medullary sheath in individual fibers of the peripheral nerves, particularly in the small bundles of nerve fibers in the calf muscles. In the popliteal space only a small number of the fibers of the main nerve trunks showed myelin degeneration. In the central nervous system there was a diffuse increase of small cells in the gray matter, especially in the lumbosacral enlargement.

7. Paterson and Greenfield: Quart. M. J. **17**:6, 1923.

The nerve roots also showed some cellular increase, but little meningeal or perivascular exudate was found. In one of the cases there were marked changes in the motor nerve cells of the ventral horns, particularly in those supplying the distal portion of the limbs, consisting of moderate chromatolysis, eccentricity of the nuclei and vacuolation of the cytoplasm. These changes were interpreted as the reaction of the cell body to degeneration of the peripheral part of the axon, and they are usually present to a greater or less degree in polyneuritis. The character of the apparent cellular infiltration of the nerve roots and the gray matter of the cord was not clearly established. The cells appeared to be derived from the sheath of Schwann in the case of the nerve roots; in the cord they suggested a glial origin rather than a lymphocytic infiltration. In the degenerated calf muscles the great increase of cells was probably the result of the multiplication of the sarcolemma nuclei. One of these patients died of intussusception, the other of a generalized tuberculosis. The authors designated the condition as erythredema polyneuritis.

In a case reported by Davis,[8] an incomplete necropsy was permitted, the liver only being examined. The microscopic examination of a small piece of this organ showed "fatty degeneration and infiltration of the liver."

In the discussion of Butler's paper before the Section on Dermatology and Syphilology at the seventy-fifth annual session of the American Medical Association, Chicago, June, 1924, E. A. Oliver reported the findings in a case coming to necropsy, as follows:

> Necrosis of the mandible. The hands and fingers were spindle-shaped, with much scarring. The skin was thick and leathery. There were: sclerosis of the cranial bones, an abscess of the tissues of the sacrum, an abscess of the left lung and cloudy swelling of the heart, liver and kidneys. There was also an accessory suprarenal.

Jenny [9] reported a fatal case with necropsy in a girl aged 27 months. The necropsy findings were double bronchopneumonia, chronic splenic enlargement, cloudy swelling of the kidneys, ascaridiasis, enteritis, atrophy of the thymus, hyperplasia of the lymphoid apparatus, hypoplasia of the medulla of the suprarenals, diffuse colloid struma partly fibroid and cardiac hypertrophy.

Parkes Weber [10] made a skin biopsy from the border of an ulcer on the foot of his patient. The examination was made for the purpose of determining whether the lesion was tuberculous. The corium was infiltrated with lymphocytes, plasma cells and fibroblasts. No giant cells were present, and no tubercle bacilli were found.

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8. Davis, Clara M.: Arch. Pediat. **39**:611, 1922.
9. Jenny: Schweiz. med. Wchnschr. **55**:645, 1925.
10. Weber, Parkes: Brit. J. Dermat. & Syph. **33**:228, 1921; **34**:111, 1922.

Butler [2] reports the microscopic findings in a biopsy taken from the hand of his patient, a boy aged 5 years. The biopsy and tissue examination were made by Michelson, who made the following report:

> The striking feature was the marked hyperkeratosis; there was no parakeratosis. The stratum lucidum was visible. There was some ballooning of the cells of the granular layer. The basal layer was intact. There was no acanthosis. In the corium there was a slight infiltrate of lymphocytes arranged in small strands or clumps. There were some fibroblasts also present in these areas. There was considerable edema of the corium but nothing in the section that was pathognomonic. The marked hyperkeratosis and the edema alone differentiated the slide from the same area in a normal child.

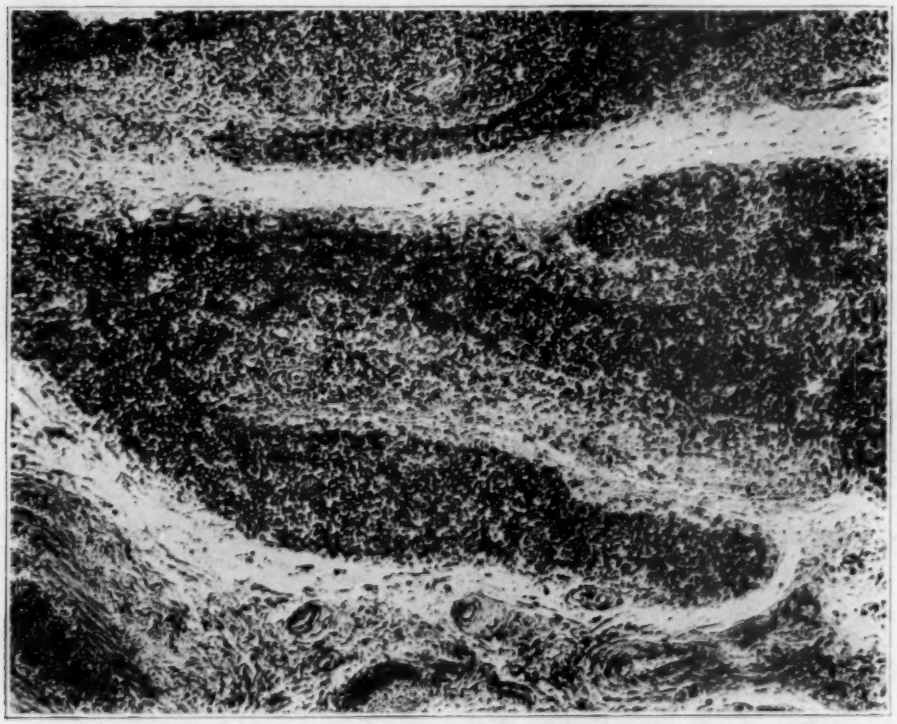

Fig. 2 (Case 1).—Section of atrophic thymus. Marked atrophy of the lymphoid tissue; very few and very small corpuscles of Hassall.

Michelson regarded the hyperkeratosis and the edema of the corium as the characteristic changes shown by his sections, and emphasized the fact that the edema alone would account for the great increase in the circumference of the fingers. A photomicrograph of the skin section accompanies this article.

As far as I can discover, these are the only accounts of necropsies and biopsies in cases of so-called acrodynia contained in the literature. They offer little on which to base any statement as to the characteristic

pathology of this affection, and throw no light on its essential nature or etiology. As the mortality in the disease is so low, it is important that any opportunity for a necropsy should be seized when the patient dies from a disease clinically diagnosed as acrodynia or erythredema, and a thorough pathologic study should be made of the material afforded by the necropsy. The solution of the pathologic and etiologic problems offered by this striking clinical syndrome will depend on the advantage taken of such opportunities, and the analysis of the pathologic findings so obtained. For this reason I consider it important to present the following pathologic study of two necropsy cases of acrodynia.

REPORT OF CASES

Two clinically typical cases of "acrodynia" or "erythredema" came to necropsy in the Pathological Laboratory of the University of Michigan during the last year from the University Clinic of Pediatrics, Dr. D. M. Cowie, to whom we are indebted for the following clinical histories.

CASE 1.—*History.*—L. B., aged 23 months, was admitted to the University Hospital, April 28, 1925, because of loss of weight, marked irritability and a rash over the body. The parents were living and in good health; there were four other living children; no children were dead, and there had been no miscarriages. One of the children, 8 years old, had tuberculosis; the other three were well. There was no other family history of tuberculosis, and none of cancer or diabetes. Birth was normal, at full term, and the child had never shown any cyanosis, and had never had convulsions. It was breast fed for three months, and then bottle fed on modified cow's milk for one year. When admitted, he would take only liquids, which had to be forced. He walked at the age of 15 months, and began to talk indistinctly at the same time. He had never talked normally. He had thirteen teeth. He had had no children's diseases and no other diseases, injuries or operations. His present illness began about Feb. 15, 1925, with a severe cold which was diagnosed as influenza, and which terminated in pneumonia. At this time the child began to eat poorly, to grow gradually weaker and to become restless. He would scream without cause, burrow his head in the pillows, and constantly move about. His hands and feet had been red and cold since the illness in February. He slept poorly, and would cry out in his sleep. About April 1, an eruption appeared on the abdomen, spreading to the neck and extremities. He would scratch himself when unclothed; and his hands and feet were especially pruritic. At times there was excessive perspiration. He would also pull out his hair. He could be kept quiet by rubbing his arms and legs. When taken ill, his weight was 35 pounds (15.9 kg.); at admission it was 22¾ pounds (10.3 kg.). He had lost no teeth.

Examination.—This showed a rather small, fairly well nourished male child, very restless, continually moving his extremities in a slow regular manner, scratching the abdomen and chest and rubbing his hands together. At times he would rub his feet and legs on the table and make a peculiar cry without any apparent cause; at other times he seemed to be in slight pain. The head was symmetrical; there was no prominence of the bosses. The hair was scant, light brown and fine; some of it had been pulled out. The head seemed tender

to touch. The child would cry at every touch, and was resistant to examination. The scalp was dry and slightly scaly. The examination of the ears was negative. There was a slight purulent discharge from both eyes. The pupils were unequal, the right somewhat more contracted than the left. They reacted promptly to light; there was no nystagmus and no exophthalmos. The teeth were in good condition; the tongue was slightly coated; the breath was fetid. The tonsils were slightly enlarged. On the face there was an irregular blotchy erythema, more marked on the left side. The neck was short, but not unusually thick. The cervical lymph nodes were enlarged. The chest was symmetrical, slightly flaring at the lower margin; there was no beading of the ribs, although there was a distinct groove. The spine showed a slight scoliosis to the right

Fig. 3 (Case 2).—Section of spleen. Marked lymphoid exhaustion of splenic follicles, showing the epithelioid-cell-like appearance of the maternal lymphoblasts and reticulo-endothelium. Characteristic of the lymphatic constitution.

in the mid-dorsal region. The heart was not enlarged. At fairly regular intervals there was an almost immediate first sound following a previous first sound. There were no murmurs. Examination of the lungs was negative and also that of the abdomen. The spleen was not palpable. There was a marked phimosis. The axillary and inguinal nodes were enlarged; the epitrochlears were not felt. The extremities showed no deformities. The knee and Achilles reflexes were much reduced; the biceps and triceps reflexes could not be obtained, likewise the cremasteric; the umbilical reflexes were present. There was a bilateral Babinski sign. The blood Wassermann test was negative.

The skin of the trunk presented a generalized reddish to copper colored maculo-papulo-vesicular eruption, which was apparently slightly pruritic; on the back the eruption was more pronounced. The backs of the hands and the dorsal surfaces of the feet showed a blotchy erythema, more marked on the palms of the hands; the soles showed slight desquamation.

The temperature on admission was 99.5 F. The urine examination was negative. The white blood cells numbered 11,200. The blood sugar was 0.116 per cent. There were 23 mg. of nonprotein nitrogen per 100 cubic centimeters.

The clinical diagnosis in the department of pediatrics was acrodynia, extrasystoles, blepharitis.

The patient was referred to the department of neurology (Dr. C. D. Camp). The condition was here diagnosed as toxic erythema, "acrodynia."

The child was also referred to the department of dermatology (Dr. Udo Wile). Here the same diagnosis of toxic erythema ("acrodynia") was made; hospitalization and tonsillectomy were advised.

Course of Illness.—Twenty-four hours after admission the child developed signs of pneumonia, and died forty-eight hours after admission. The final clinical diagnosis was acrodynia and pneumonia.

Necropsy (April 30, 1925, 7:00 p. m.).—L. B., a male infant, 23 months of age, was of normal size for his age. General nutrition appeared good. The skin was of fine texture. Over the trunk there was a maculopapular eruption, the papules averaging pinhead size. They were yellowish brown, and were both discrete and confluent. The palms and soles showed desquamation. The hair was brown and of very fine texture. No edema was present; the skin did not pit on pressure. Panniculus adiposus was moderate. There was marked phimosis. The meninges of the cord and brain showed marked edema. On section the brain substance showed marked edema and congestion; it was described as "extremely wet throughout." The cerebrospinal fluid was greatly increased. Examination of the abdomen was negative. There was a small amount of clear yellow fluid in the pleural cavities. The thymus was very small, with two distinct cervical lobes; on section it appeared to consist entirely of lymphoid tissue. The heart and large vessels showed no pathologic conditions. The lungs showed marked congestion and edema, with scattered areas of purulent bronchopneumonia, more marked on the left side, the lower lobe presenting the picture of a lobar pneumonia. The bronchial, mediastinal and cervical lymph nodes were enlarged. The mucous membranes of the mouth were pale. The tonsils were moderately enlarged. The thyroid was very small; on section, it showed uniform distribution of the colloid. There was no fluid in the abdomen. The spleen was of normal size, with patchy thickenings of its capsule. The liver was slightly enlarged, showing marked congestion. No pathologic changes in the abdominal organs were visible to the naked eye, except hyperplasia of the lymphoid tissue of the intestines. The suprarenals were hypoplastic, showing slight lipoidosis. The kidneys were markedly congested. The pelvic organs were normal.

Microscopic Examination.—The meninges of the cord and brain showed marked congestion and edema. In the cerebral meninges there was a definite proliferation of the reticulo-endothelial cells, giving the picture of a slight productive meningitis, but there were no inflammatory infiltrations. The anterior and posterior horn cells were well preserved, and the nerve roots were normal. No degenerative changes were found in the nerve cells in the cord or brain. The central canal was moderately dilated. The pituitary and pineal bodies were normal. The thyroid showed slight increase in colloid for age.

The thymus showed marked atrophy of the lymphoid tissue resembling an irradiated thymus. There was very little lymphoid tissue, and the corpuscles of Hassall were relatively few and very small. The myocardium was hypoplastic; there were moderate subepicardial fatty infiltration and slight subendocardial fatty degenerative infiltration (slight tiger heart). The intima of the aorta showed slight lipoidosis. The lungs showed marked congestion and edema, with localized areas of atelectasis and an old aspiration (meconium) bronchopneumonia in a stage of organization and epithelial regeneration. Many foreign body giant cells surrounding yellowish-brown granular material (meconium) were present. There was no blood pigment. In the base of each lung there was an acute fibrinopurulent bronchopneumonia, confluent in large

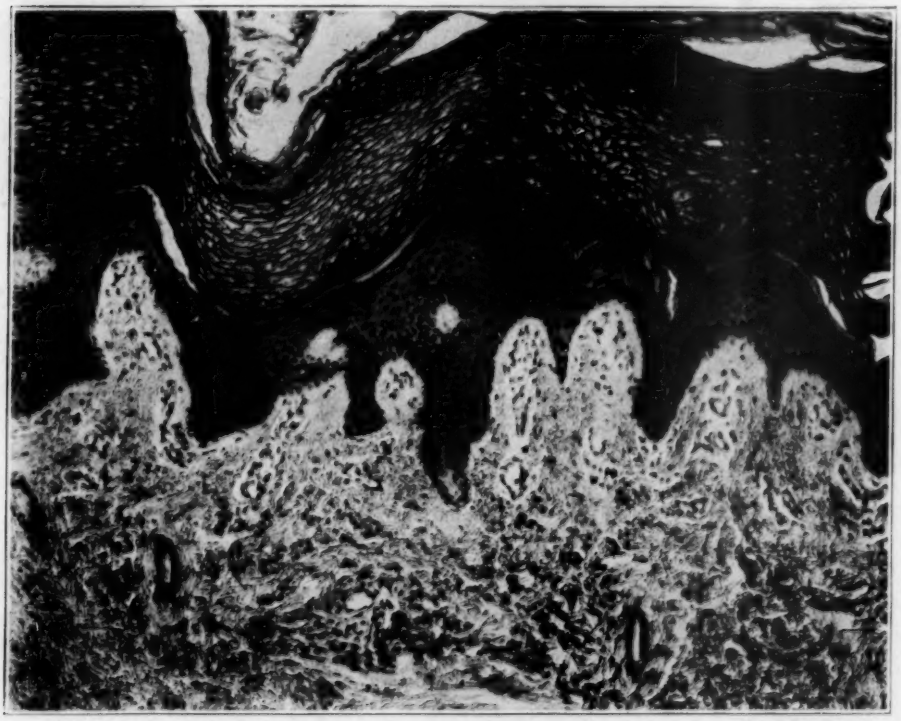

Fig. 4 (Case 1).—Section of skin from abdomen, showing marked hyperplasia and hyperkeratosis of the epidermis, with marked dilatation and hypertrophy of the capillaries of the papillary layer, with some perivascular reticuloendothelial proliferation. There is no edema of the corium; the slight separation and crowding of the collagenous fibrils is purely an artefact due to fixation and cutting.

patches. The bronchi throughout both lungs showed an early purulent bronchitis. The bronchial nodes were hyperplastic, much congested and edematous and showed marked lymphoid exhaustion of the germ centers. The spleen showed a marked lymphoid atrophy, with relative increase of the stroma and a marked passive congestion. The germ centers showed marked lymphoid exhaustion, almost wholly devoid of lymphocytes, the large pale lymphoblasts

and reticulo-endothelial cells giving the centers an appearance closely resembling that of miliary tubercles. The reticulo-endothelium of the blood spaces was hyperplastic. There was no evidence of excessive hemolysis. The stomach, small and large intestines presented throughout a slight acute catarrh, more marked in the duodenum, with marked hyperplasia of the solitary lymph nodes and Peyer's patches. The lymphoid tissue of the appendix was hyperplastic. Throughout the lymphoid tissues of the alimentary tract the germ centers showed the same extreme lymphoid exhaustion seen in the splenic follicles. The mesenteric nodes were hyperplastic and showed the same lymphoid exhaustion of the germ centers. The reticulo-endothelium of the sinuses was hyperplastic. The pancreas presented no pathologic condition except that of passive congestion. The liver showed a simple atrophy, with few scattered fat

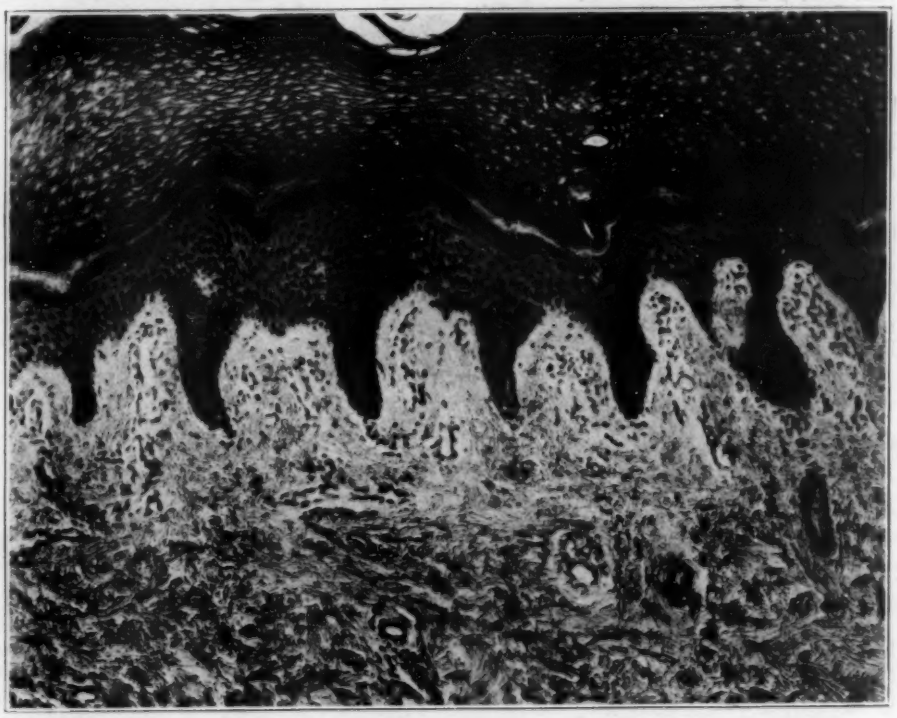

Fig. 5 (Case 2).—Section of skin from chest wall. Changes are identical with those in figure 4, but the rete is slightly more heavily pigmented.

droplets in the cells, and a passive congestion. The gallbladder was normal. The suprarenals were hypoplastic, the medullary portions especially so; there was little medullary tissue. The cortex showed marked passive congestion. The kidneys were congested, and there was slight cloudy swelling. The retroperitoneal lymph nodes were hyperplastic, with exhausted germ centers and hyperplastic reticulo-endothelium in the sinuses. There was no evidence of hemolysis in the lymph nodes or hemolymph nodes. All adipose tissue showed a return to the primitive fat lobule type; the majority of the cells stained red with eosin; the fat droplets were mostly small and scattered, with here and there a large droplet. The microscopic appearances of the genital organs,

testes, prostate, seminal vesicles and urinary bladder were negative. The examination of the peripheral nerves and sympathetic nerves and ganglions from various parts of the body revealed no evidence of the existence of a polyneuritis. No inflammatory infiltrations and no evidence of degeneration were found anywhere in the nerve trunks. In the skin a reticulo-endothelial proliferation was seen about some of the small nerve trunks lying near the sweat glands. The ganglions of the solar plexus region and the perisuprarenal ganglions appeared hypoplastic.

Skin.—Skin was taken from the abdomen, trunk, hands and feet. The microscopic changes were found to be practically identical in all parts. There was marked hyperkeratosis with scaly desquamation of the horny layer; the

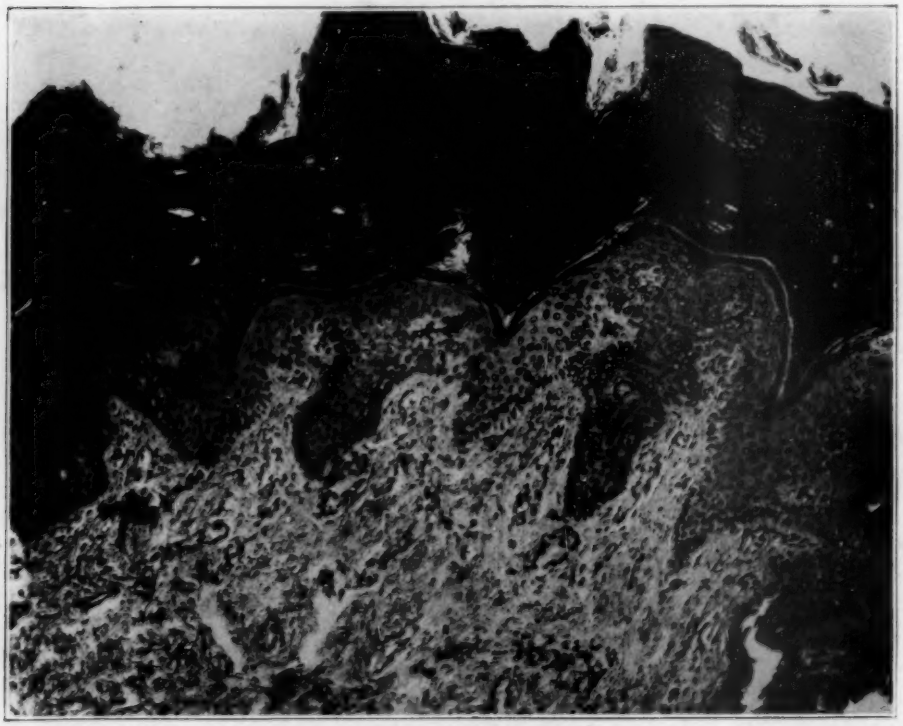

Fig. 6 (Case 2).—Skin from sole of foot, showing marked hypertrophy, hyperkeratosis and desquamation of the epidermis, capillary dilatation and hypertrophy, and reticulo-endothelial hyperplasia. There is no edema; the slight spaces are purely artefacts.

epidermis was hyperplastic, from two to four times its normal thickness, the horny layer forming from one-half to two-thirds the entire thickness of the epidermis. The rete cells showed slight pigmentation; a few chromatophores were found in the upper portion of the papillary layer of the corium. The papillae were enlarged and lengthened; the capillaries of the papillary layer were unusually prominent, the lumina dilated and the endothelium hypertrophic. The perivascular reticulo-endothelium was hyperplastic, the nuclei increased and staining deeply. There was no perivascular inflammatory infiltration and

only a slight perivascular edema. There was no generalized edema of the corium or the subcutaneous tissues, but there was some serous atrophy of the subcutaneous adipose tissue. There were no inflammatory infiltrations about the hair follicles, sweat glands or nerve trunks, although the reticulo-endothelium about these was increased. The skin of the thorax showed a more marked hyperkeratosis with more marked scurfy desquamation than that over the abdomen, and the reticulo-endothelial proliferation was more marked. Likewise, the rete in the skin from the thorax showed more pigment. The sweat glands in the skin from the abdomen and thorax were dilated and appeared hypertrophic; the sebaceous glands were very small. In the skin from the sole of the foot, all of the changes mentioned were less marked.

Pathologic Diagnosis.—The final pathologic diagnosis was: acute fibrinopurulent lobular pneumonia of both lungs, most marked in the right lower lobe; older localized organized meconium aspiration pneumonia; hypoplastic lymphatic constitution; fibroid atrophy of the thymus; hypoplasia and lipoidosis of the suprarenals; hyperplasia of the bronchial, mediastinal, mesenteric, intestinal and retroperitoneal lymph nodes, with marked exhaustion of the germ centers; acute catarrhal gastro-enteritis; marked congestion and edema of the meninges, brain and cord; atrophy of the fat tissues; hyperkeratosis and parakeratosis; erythema of the skin, with perivascular reticulo-endothelial proliferation in the papillary layer and corium (so-called "acrodynia" or "erythredema," "Swift-Feer disease").

CASE 2.—*History.*—L. P., a boy, 10 months old, was referred on Aug. 18, 1925, to the pediatrics clinic (Dr. D. M. Cowie) of the University Hospital, by Dr. E. P. Russell of Battle Creek, Mich., with the clinical diagnosis of acrodynia. The parents were living and well. There was no history of carcinoma or tuberculosis. Four other children were living and well. Birth was normal. The patient had never had convulsions. He was breast fed, and still nursing. His development apparently was normal. There was no history of exanthems. He had been well until the middle of May, when he began to have a moderate diarrhea, followed by pain over the gastric region, and a red rash. His fingers became pink, and the rash spread to the face. His face and hands were cold. Some photophobia was present. He had never vomited.

Physical Examination.—On entrance examination showed an apparently well-nourished child, apparently well. He did not seem irritable. There was no photophobia, and no tendency to bury his head in the pillow or to assume a jack-knife position. Over the trunk and extremities there was a nondescript papular eruption, apparently pruritic. The fingers and hands were pink, with occasional small vesicular lesions and a slight desquamation between the fingers. The toes and feet appeared normal, except for slight desquamation between the toes. There was no unusual perspiration. The pupils were equal. The reflexes were normal. The entrance examination showed no evidence of acrodynia except the skin changes, and nothing else abnormal except a temperature of 101 F., for which there was no apparent cause. Otherwise the child appeared well. Examination of the lungs was negative.

Course of Illness.—Two days after entrance he presented a typical picture of acrodynia. He became irritable, and continually chewed his fingers, which consequently took on a water-soaked appearance. He whined continually, crying out occasionally as if in pain, and attempting to grab his feet. Much of his time was spent in the knee-chest position, with his head buried in the covers, but tossing about a good deal, sometimes suddenly throwing himself

down with his head in the covers. He was exceedingly thirsty, asking for water continually. His stools were semifluid. The temperature was about 100 F. The rash on the thorax and extremities remained unchanged. He was referred to the department of dermatology, where the diagnosis of acrodynia was verified. Neurologic examination showed only irritability and vasomotor disturbances of the hands and feet. By the fourth day after entrance his condition seemed worse; he was evidently losing weight in spite of forced feeding. The stools were liquid, and his temperature ranged about 101 to 102 F. On the seventh day after entrance, he had lost markedly in weight, and there was some evidence of dehydration. The stools remained liquid, although not so frequent. The right ear appeared congested, with some bulging. Paracentesis yielded no

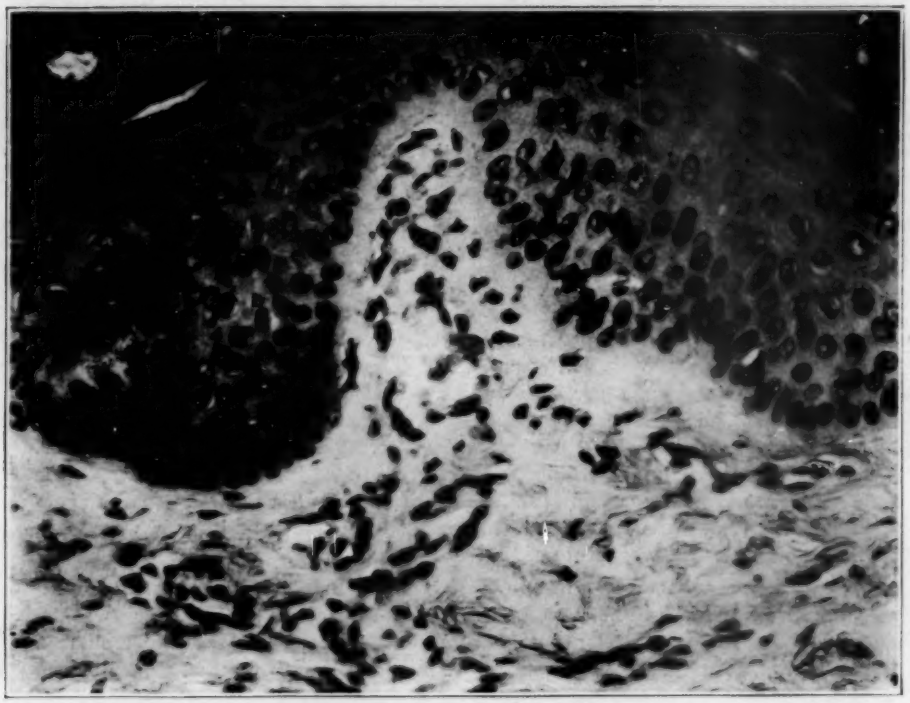

Fig. 7 (Case 1).—Higher power photomicrograph of skin, showing hypertrophic capillaries of the papillary layer.

pus. During the day he suddenly became cyanotic, with feeble pulse and cold hands. The temperature was 105.4 F., and the patient appeared listless and markedly dehydrated, although the stools were less frequent, and he had not vomited. Epinephrin was administered, and the stomach lavaged with soda solution, and 8 ounces of water left in the stomach. Following this, his color improved, but later in the afternoon, he became very cyanotic again, with feeble and rapid pulse. Two grains of caffein sodium benzoate were given by hypodermic injection, and he became much brighter but very restless. About five hours later, his respirations became very rapid, and he did not respond to further treatment, dying about 2:35 a. m., August 25.

Necropsy (7:20 a. m., Aug. 26, 1925).—This was an apparently well-nourished male infant, large for its age. His neck was short and thick. There were no signs of rickets. The face and finger nails were cyanotic. The hands were pink and puffy; the feet also were puffy. The forehead had a brownish pigmentation. The mucous membranes were cyanotic. The lower extremities pitted on pressure. Panniculus adiposus was moderate. Two central lower incisors and the upper lateral incisors had erupted. The hair was light brown and fine. The meninges of the cord were edematous. The cerebral meninges were very wet, with marked congestion and edema. The brain showed extreme congestion and edema. There was no free fluid in the abdominal or thoracic cavities. The intestines were enormously distended. The thymus weighed 10 gm.

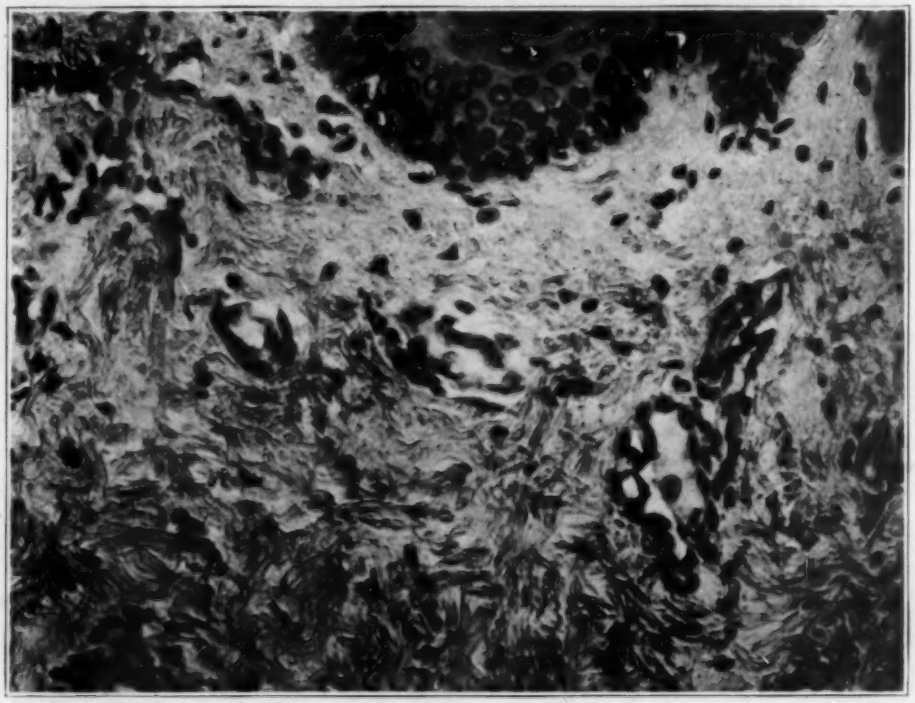

Fig. 8 (Case 2).—Higher power photomicrograph of skin, showing hypertrophic capillaries and absence of edema.

The heart was normal. The lungs showed marked congestion and edema and acute purulent bronchitis. The tonsils were not enlarged. The thyroid was of normal size, with colloid content for age. The spleen was small and soft. The follicles were easily seen; they were enlarged. The lymph follicles of the gastro-intestinal tract were hyperplastic. There was no intestinal ulceration. Appearances of subacute gastro-enteritis were most marked in the duodenum. The mesenteric lymph nodes were markedly hyperplastic. The pancreas was normal. The liver was normal in size and showed slight fatty change. The suprarenals were markedly hypoplastic, particularly the medullary substance. There was no increase of lipoids. The kidneys showed congestion and slight cloudy swell-

ing. The aorta was hypoplastic. The retroperitoneal lymph nodes were hyperplastic. The pelvic organs were normal.

Microscopic Examination.—In the brain and meninges there were marked congestion and edema. There was a slight increase in the number of wandering cells in the edematous meninges, and marked proliferation of the reticuloendothelium. Marked perivascular edema was present throughout the brain. There were no degenerative changes in the nerve cells and no inflammatory infiltrations. The central canal of the cord was markedly dilated, with distortion of the butterfly figure. There was marked perivascular edema in the cord, but no degenerative changes in the nerve cells and no inflammatory infiltrations. The nerve roots were normal. The pituitary body was congested; the pineal, normal. The thymus showed marked lymphoid atrophy with fibrosis. The

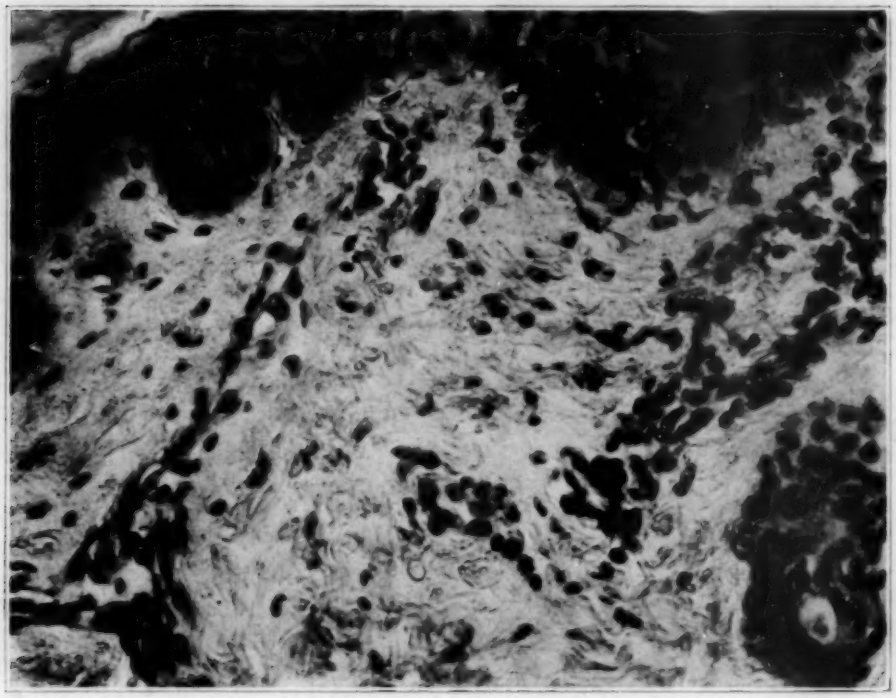

Fig. 9 (Case 1).—Skin from thorax, showing reticulo-endothelial hyperplasia along the capillaries.

corpuscles of Hassall were few and relatively small. The thyroid showed a normal colloid content for the age of the child. The trachea and larynx were congested, with slight edema and acute catarrhal inflammation. The tongue and esophagus were normal. The tonsils showed hyperplastic germ centers with exhaustion of lymphocytes. The lungs showed extreme congestion and edema, with localized areas of atelectasis and acute purulent bronchopneumonia. The heart showed slight fatty degenerative infiltration. The spleen showed lymphoid atrophy with marked exhaustion of the germ centers and degeneration and necrosis of the lymphoblasts. There was relative increase of the stroma, and passive congestion. The stomach and intestine showed a subacute catarrhal

inflammation with hyperplasia of the lymphoid tissue, lymphocyte and plasma cell infiltration of the stroma of the villi. The liver showed passive congestion and slight cloudy swelling, with hyperplasia of some of the rudimentary lymph nodes. The gallbladder and pancreas were normal. The suprarenals were hypoplastic, with excessive lipoidosis. The kidneys showed congestion and slight cloudy swelling; the pelves were normal. The lymph nodes showed marked lymphoid hyperplasia, increase of sinus reticulo-endothelium, and exhaustion of the germ centers. Adipose tissues showed an abundance of fat cells. The pelvic organs were normal. The bone marrow showed lymphocyte exhaustion. No evidence of increased hemolysis was present in the spleen or lymphoid tissues. Examination of the peripheral and sympathetic nerves was negative. There was no evidence of a polyneuritis.

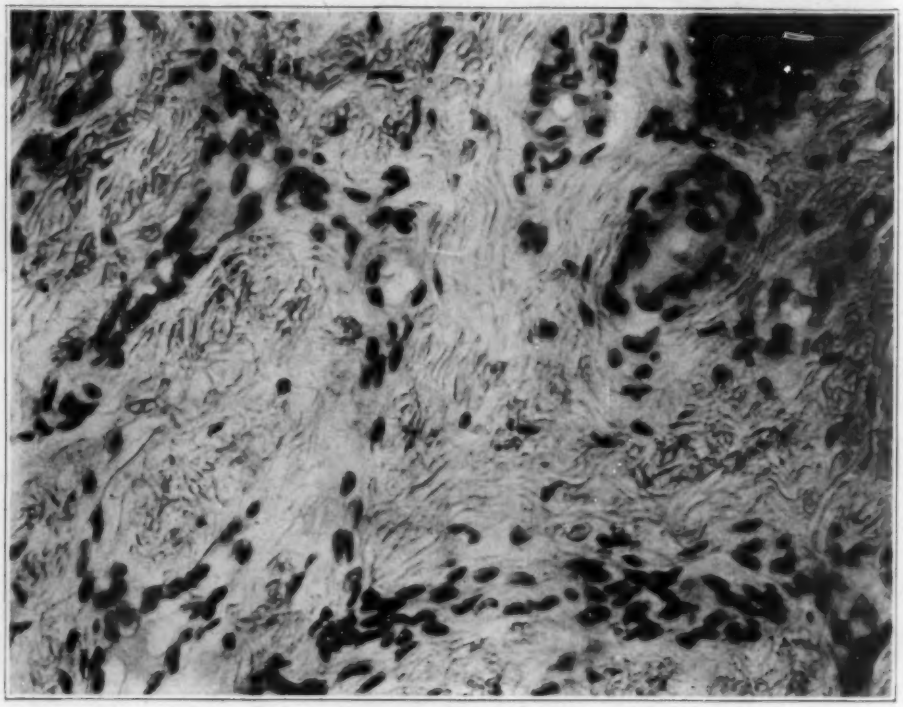

Fig. 10 (Case 2).—Hypertrophic capillaries in corium.

Skin.—The skin taken from the abdomen, trunk and hand showed the same conditions as in Case 1; namely, marked hyperkeratosis and parakeratosis, hyperplasia of the epidermis and papillary layer, dilatation and hypertrophy of the capillaries, proliferation of perivascular reticulo-endothelium, slight pigmentation of the rete, hypertrophy of the sweat glands and serous atrophy of the subcutaneous fat. There was no edema of the corium or papillary layer, and no inflammatory infiltrations of the cutaneous nerve trunks.

Pathologic Diagnosis.—The pathologic diagnosis was: terminal bronchopneumonia; pulmonary congestion, stasis, edema and localized atelectasis; hyperkeratosis and erythema of the skin (clinical diagnosis of acrodynia);

serous atrophy of the panniculi; extreme edema of the meninges, cord and brain; dilatation of the central canal of the cord; fibroid atrophy of the thymus; hyperplasia of all lymphoid tissues, with exhaustion of the germ centers; hypoplasia of the heart and aorta; lymphatic constitution; subacute catarrhal enterocolitis; passive congestion, atrophy and slight parenchymatous degeneration of all organs.

PATHOLOGIC SUMMARY OF THE TWO CASES

Cause of Death.—Acute fibrinopurulent bronchopneumonia was the cause in both cases. In Case 1 this was associated with an older organizing aspiration pneumonia dating either from birth (meconium) or the

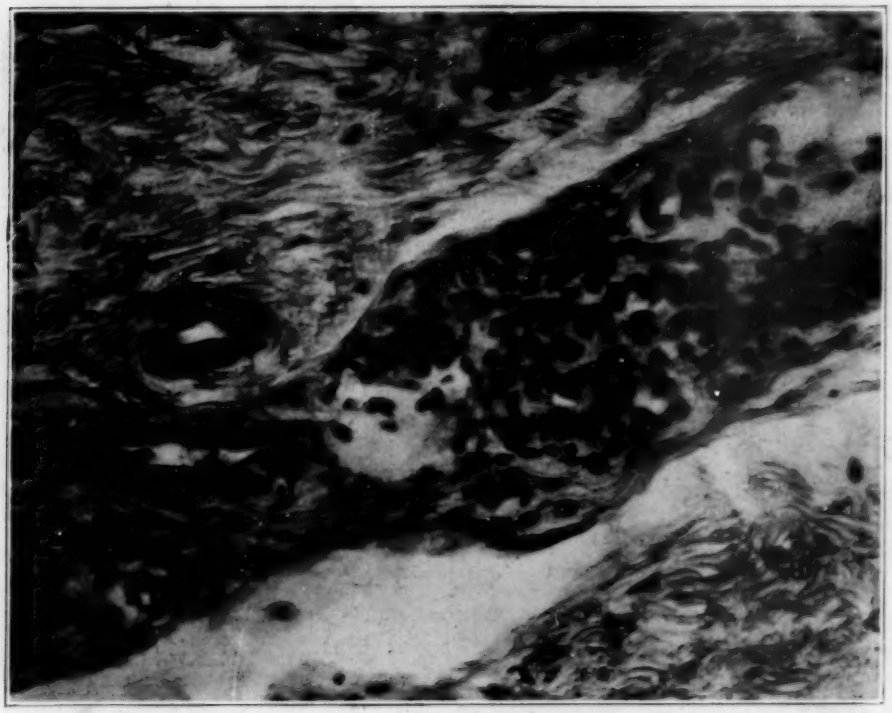

Fig. 11 (Case 2).—Reticulo-endothelial hyperplasia about sweat glands.

illness in February. In Case 2 the pneumonia was acute and undoubtedly terminal. There were no septic processes in the tonsils or in the middle ears.

Gastrointestinal Tract.—Case 1 showed an acute catarrhal gastro-enteritis; Case 2, a more severe and subacute gastro-enteritis, most marked in the duodenum in both cases.

Central Nervous System.—There was extreme edema of the meninges and brain. The meninges and brain were very wet. There was proliferation of the meningeal and perivascular reticulo-endothelium.

No degenerative changes were present in the nerve cells or fibers of the brain or cord. There was no gliosis. There was dilatation of the central canal of the cord in both cases, very marked (hydromyelia) in Case 2. No inflammatory changes were found in the brain or cord or in the nerve roots.

Peripheral Nerves.—No inflammatory or degenerative changes were found in the peripheral nerves in either case. There was no evidence of a polyneuritis. There were no degenerative changes in striped muscles. Only a slight reticulo-endothelial proliferation occurred around a few nerve trunks in the skin.

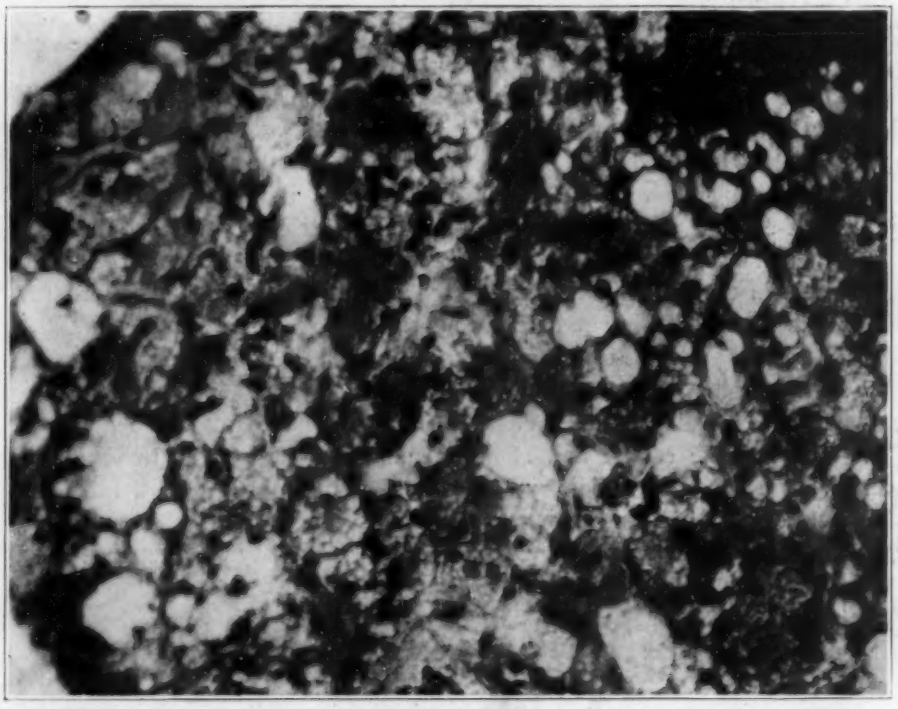

Fig. 12.—Retroperitoneal adipose tissue. Removal of fat droplets, and partial return to primitive fat-lobule appearance.

Endocrine Organs.—The pituitary and pineal bodies and the testes were normal. The thyroid showed a slight increase in colloid in Case 1; it was normal in Case 2. The thymus in both cases showed marked fibroid atrophy. The suprarenals in both cases showed marked hypoplasia of the medullary portion. There was hypoplasia of the chromaffinic tissue in the suprarenals and ganglions.

Constitutional Stigmas.—Both cases presented the features of the hypoplastic lymphatic constitution. There was marked hyperplasia of

all lymph nodes, with marked exhaustion of the germ centers, hypoplasia of the suprarenals, heart and aorta. The tonsils were moderately enlarged.

Skin.—There were marked hyperkeratosis and hyperplasia of the epidermis, slight pigmentation of the rete, marked capillary dilatation and hypertrophy, perivascular reticuloendothelial proliferation, no inflammatory infiltrations, no edema of the papillary layer or corium, marked hypertrophy and dilatation of the sweat glands.

Adipose Tissue.—There was serous atrophy. Removal of fat was followed by return to a condition resembling that of the primitive fat lobules.

COMMENT

Acute infection of the respiratory tract was present in both cases; in one case, an older process. Both cases showed gastro-enteritis. No other infective processes were present. Both showed marked features of the hypoplastic lymphatic constitution. In both cases there were extreme congestion and edema of the central nervous system, with reticulo-endothelial proliferation. In both cases no evidences of a polyneuritis were present. Both cases showed the same pathologic changes in the skin in the form of hyperkeratosis, slight pigmentation, chronic erythema without edema, hypertrophy of the sweat glands and perivascular reticulo-endothelial proliferation. Both cases showed inanition in the serous atrophy of the adipose tissues.

The essential pathologic changes in these two cases would appear to be: extreme edema and slight meningeal irritation of the central nervous system, chronic erythema of the skin with hyperkeratosis, hypertrophy of the epidermis and sweat glands, with slight pigmentation of the rete, occurring in children of the hypoplastic lymphatic constitution, with associated or terminal respiratory infections and gastro-intestinal catarrh and inanition.

These two cases, therefore, do not support the theory of a polyneuritis as the essential feature of the disease; neither do they justify the use of the term erythredema as a fitting designation, as they showed no edema of the corium. They do not present any evidence as to a specific infectious etiology; they likewise show no relationship between tonsillar disease and the syndrome.

The changes in the skin and central nervous system suggested to me at once the pathology of the early erythema stage of pellagra. The changes in the skin are also identical with those seen in certain forms of light sensitization, xeroderma and fagopyrism. They are also identical with certain stages of roentgen-ray and ultraviolet ray erythemas. The entire anatomic picture in these two cases suggests either a food deficiency or a toxic state acting on persons of the

hypoplastic constitution, affecting the reticulo-endothelial system of meninges and skin, the vegetative nervous system and possibly leading to a light sensitization. May it not be, as was early suggested by Byfield, a condition closely related to pellagra, perhaps an infantile variety of that affection? Other necropsy cases must be collected and studied before this question can be settled. In the meantime, it would be better to call the condition Swift's disease than to designate it by terms that apply so little to it as do "acrodynia" or "erythredema."

FAT REPLACEMENT OF THE GLYCOGEN IN THE LIVER AS A CAUSE OF DEATH *

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AND
H. A. SINGER, M.D.
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During efforts to produce a cirrhosis of the liver in animals with alcohol, as well as during experiments designed simply to ascertain the effects of alcohol on its structure, an accumulation of the fat in the liver cells has been found so commonly as the main alteration that a relation between alcohol and fatty changes in the liver has long been recognized.

Rosenfeld [1] furnished rather conclusive evidence of this relation by withholding glycogen-forming foods from the diet of animals fed with alcohol and observing fatty changes of the liver as a sequence. In discussions of this subject, it has long been customary to refer to the demonstration of fatty changes by Friedenwald [2] as the chief effect in rabbits from long-continued administration of alcohol.

The conclusions of Formad [3] based on postmortem examinations of the bodies of 250 chronic alcoholics, and the presence of large fatty livers in 90 per cent of these has more recently been corroborated by Fahr [4] from an examination of 309 such bodies. Fahr states definitely that a fatty liver is the most constant change with chronic alcoholism, and similar statements by others [5] are not wanting.

Although, as first stated, acceptance of this association of alcohol with marked fatty changes of the liver has in these various ways become general, no such agreement has as yet been arrived at with regard to symptoms enabling an estimate clinically of the degree to which the

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* From the Pathological Laboratories of Rush Medical College, University of Chicago, and the Cook County Hospital.

1. Rosenfeld, G.: Fettbildung, Ergeb. d. Physiol. **2**:50-94, 1903; Beiträge zur pathologie des Alkohols, Zentralbl. f. Med. **21**:1049-1060, 1900.

2. Friedenwald, J.: The Pathologic Effects of Alcohol on Rabbits, J. A. M. A. **45**:780-784, 1905.

3. Formad, H. F.: The "Pig-Backed" or Alcoholic Kidney of Drunkards, Tr. Am. Assn. Physicians **1**:225-236, 1886.

4. Fahr, T.: Zur Frage des chronischen Alkoholismus, Verhandl. d. deutsch. path. Gesellsch. **13**:163-169, 1909.

5. Moebius, E.: Die Fettleber, Deutsch. Klin. **2**:240-241, 1850. Schüppel, O.: Fettleber, Hepar Adiposum, Handl. d. Spec. Path. (Ziemssen), Leipzig 8:389-419, 1878. Weichselbaum, A.: Discussion, Verhandl. d. deutsch. path. Gesellsch. **13**: 169, 1909. McJunkin, F. A.: The Human and Animal Liver After Alcohol, Arch. Int. Med. **19**:786-800, 1917.

liver has suffered such alterations, and this notwithstanding the attention this phase of the subject has received since Louis [6] first called attention to marked fatty changes of the liver and especially its association with tuberculosis. That such hepatic disease may be encountered in the bodies of persons who are apparently well has been commented on by Frerichs [7] and Begbie,[8] and the absence of symptoms, except those connected with its increased size, has been the subject of comment by many writers [9] in considering marked fatty degeneration of the liver.

Some authorities have emphasized the greater ease with which persons with such hepatic disease succumb to infections and infectious diseases. Gilbert and Lereboullet [10] also have pointed out this bearing, but they have gone much further and frankly challenged the laissez faire attitude of clinicians regarding the absence of distinctive symptoms, asserting that competent study should demonstrate impaired function of livers so diseased.

One of us (E. R. L.) has been greatly impressed for many years by encountering huge fatty livers at rare intervals during routine postmortem examinations; these were frequently found in the bodies of small women whose consumption of whisky or similar liquors (brandy) was inordinate. Little else was found within the bodies to explain death, which was often sudden or unexpected and not the result of delirium tremens. Two examples of such deaths follow.

CASE 1.—J. C., a white woman, aged 45, entered the Cook County Hospital, in the service of Dr. Hassin, March 21, 1924, at 2:00 p. m., and died much to the surprise of those in attendance twelve hours and fifteen minutes later.

The preliminary diagnosis was neurasthenia and the assignment was "neurology." The following was written after death: "This ambulatory patient complained on entrance of vague gastric symptoms, generalized aches and pains, and occipital headache. A superficial examination revealed nothing abnormal. The pulse was strong, the temperature normal and she was resting quietly. At 9:00 p. m., when I visited her, she was apparently in good condition, and death was unexpected." After 1:30 a. m., the nurse noted groaning respirations, a weak pulse and cyanosis of the face, and these continued until death at 2:15 a. m. After death, it was learned that she had been drinking heavily, and was nervous and weak.

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6. Louis, P. C. A.: Recherches anatomiques, pathlogiques, et therapeutiques sur la phthisie, trans. by Charles Cowan, Washington, D. C., 1836.

7. Frerichs, F. T.: Diseases of the Liver, trans. by Charles Murchison, New York **1**:196-219, 1879.

8. Begbie, J. W.: Fatty Liver, in Reynolds: A System of Medicine, London **3**:360-370, 1871.

9. Addison, T.: Observations on Fatty Degeneration of the Liver, Guy's Hosp. Rep. **1**:476-483, 1836. Bamberger, H.: Die Fettleber; Schmidt's Jahrb. d. ges. Med. **79**:298-300, 1853. Murchison, C.: Clinical Lectures on Diseases of the Liver, New York, 1868, pp. 43-52. Rolleston, H. D.: Diseases of the Liver, Gallbladder and Bile Ducts, London, pp. 426-433, 1912.

10. Gilbert, A., and Lereboullet, F.: La steatose latent des alcoholiques, Bull. et mém Soc. med. d. hôp. de Paris **19**:577-585, 1902.

Anatomic Diagnosis.—The diagnosis was: marked fatty changes of the liver; moderate edema of the leptomeninges; hyperplasia of the spleen; marked passive hyperemia of the kidneys and bowel lining; sclerosis of the aorta and front mitral leaflet; submucous minute petechial hemorrhages of the pancreatic duct; varicose veins of the lower extremities; slight anasarca (ankles); acute catarrhal conjunctivitis; fibrous adhesions between the liver and diaphragm, spleen and diaphragm, and spleen and liver.

The liver weighed 2,900 gm. and presented the well-known alterations of "large fatty liver," grossly and microscopically. Chemical examination of the abdominal viscera and of the gastric and intestinal content failed to disclose the presence of alcohol or any other poison.

Case 2.—J. D. C., a white man, aged 54, entered the Cook County Hospital in the service of Dr. Hamberger, May 24, 1924, at 9:30 p. m., with a diagnosis of chronic alcoholism and cirrhosis of the liver. He was seen by the resident physician of the ward at 10:35 p. m., and appeared to be in fairly good condition, but

Ratio of Weight of Liver to That of Body

Patient	Age in Years	Sex	Body Weight in Kg.	Weight of Liver in Gm.	Ratio of Liver to Body Weight
M. S.	28	F	39.46	3,263	1 to 12.09
J. W.	40	M	66.14	4,148	1 to 15.91
C. G.	43	F	41.81	2,980	1 to 14.37
M. M.	43	F	51.50	3,200	1 to 16.08
J. F.	54	M	57.16	3,120	1 to 18.32
J. O.	45	F	55.68	2,900	1 to 19.86
G. K.	31	M	62.73	3,150	1 to 19.51
J. B.	31	M	60.00	2,991	1 to 20.02
J. D. O.	54	F	56.00	2,500	1 to 22.22
L. T.	41	M	53.97	3,090	1 to 17.46

he died abruptly about ten minutes later. A brother said the patient had been addicted to alcohol for many years, recently had used "moonshine," and for about a week had complained of weakness, tremor, nausea and epigastric distress.

Anatomic Diagnosis.—The diagnosis was: marked fatty changes of the liver; edema of the leptomeninges; moderately lessened "lipoid" of the suprarenal cortices; cholesterol deposits in the liver and kidneys; almost empty bowel; hypertrophy of the heart; passive hyperemia of the spleen, kidneys, liver and bowel; calcified tracheobronchial lymph glands; retention cysts of the left kidney; left focal fibrous pleuritis; fibrous localized perihepatitis; lessened colloid (atrophy) of the thyroid gland.

Chemical examination of 254 Gm. of stomach and content yielded 0.34 cc. of alcohol, but no other poison.

In the table, the age, sex, and ratio of the liver to body weight are given.[11] A much larger series could easily be tabulated by using more necropsy records, but it is believed that these few from recent necropsies answer the purpose. It is of special significance that of the eleven, five were women.

About one-half hour before the death of one patient, a convulsion occurred with frothing at the mouth and cyanosis; another was subject to "fits," but had none during the three days he was in the hospital.[12]

11. The normal ratio of the liver to the body weight is from 1:31 to 1:36. Vierordt, H.: Daten und Tabellen für Mediziner, Ed. 3, Jena, 1906.

12. The term "whisky fits" has long been in common use by policemen.

For one of these patients, the clinical diagnosis was delirium tremens, but when death occurred this had largely cleared up; for six, the diagnosis was chronic, and for two acute, alcoholism; for two cirrhosis of the liver. The enlargement of the liver was usually noted clinically, once thought to be due to secondary growths from a rodent ulcer of the face, once regarded as hypertrophic cirrhosis. In six patients there was jaundice—marked in only one.

Some bronchopneumonia developing during the last days in the hospital, due to poor pulmonary ventilation and infection of dependent parts of the lungs, was present in a number of bodies.

In considering the way in which death is brought about in cases such as these, acute poisoning from alcohol is excluded by the absence of coma, for alcohol causes death in an acute condition as does ether and similar anesthetics. Drinking of a large amount of alcohol, as occurs at times on a wager, is followed by stupor, then coma and death. Delirium tremens may also be excluded, although, as stated, one of the patients had delirium tremens shortly before death. It is of some significance that the lining of the stomach in deaths such as these has no hemorrhages characteristic of delirium tremens,[13] nor are such large fatty livers common with delirium tremens, nor is cirrhosis of the liver, as Fahr [4] has also emphasized.

Fahr, in discussing the cause of death from alcohol, mentions the possibility of alterations in the vagus and sympathetic nerves and ganglions within the heart, but his comments do not especially concern the type of disease we are dealing with in which the ratio of liver weight to that of the body is so large, nor does he present evidence of such changes in nerves or ganglions. That alcohol is concerned with changes in the peripheral and central nervous system is generally accepted in connection with both alcoholic neuritis and the Korsakoff syndrome. In another place,[14] one of us (E. R. L.) has an account of gross alterations of the brain with delirium tremens, changes not encountered in the bodies of persons whose deaths are accompanied by the circumstances under discussion.

In these the most conspicuous features are the huge size of the liver and the difficulty in finding liver cells microscopically which from their number and size seem to possess any evidence of glycogen storage consistent with life. This marked fatty infiltration has played a part so important in the classroom work of teaching pathology and has been the subject of so much illustration and description ever since instruction in

13. Hirsch, E. F.: The Gastric Mucosa in Delirium Tremens, Arch. Int. Med. **63**:354, 1914.

14. Sceleth, C. E., and Beifeld, A. F.: Cerebral Edema (Wet Brain) in Chronic Alcoholism, Am. J. Med. Sc. **149**:886, 1915.

such details of disease has been practiced, that the alteration may be regarded as familiar to all physicians.

It will be recalled that large globules of fat replace the cytoplasm of the liver cells, and that the nucleus and remaining cytoplasm form a thin crescent ("signet ring") about a part of the periphery of the fat. It is obvious that in such cells there is no considerable store of glycogen. Such livers as these are so loaded with fat that thin slices float in water. A cirrhosis may be present, but is usually not marked. The little present may not be noted grossly, the irregularities otherwise denoting it being smoothed out by the accumulation of fat.

It seems to us that any attempt to explain unexpected deaths such as these must include absence of an adequate store of glycogen to meet the requirements of the body for glucose. In only one of these ten patients was chemical examination of the blood made, but in that instance, the sugar, 67 mg. per one hundred cubic millimeters, was significantly low.

Sheep becoming carnivorous when kept in abattoirs and developing an aversion for herbivorous foods, waste and die with fatty livers twice their normal size,[15] and Williams [16] has reported the death of a diabetic patient who had received no insulin, the death, "due to inanition," being accompanied by hypoglycemia and convulsions.

When death is contributed to by hypoglycemia following the use of insulin, convulsions have also been observed; they were not noted, except as mentioned, in the illnesses of the ten patients with these large livers.

It is well known that during heavy drinking of alcoholic beverages, food consumption is frequently reduced to a minimum, and that vomiting may also lessen the value of that taken. The alcohol drunk is oxidized, and the question naturally arises: Is the oxygen available from respiration inadequate to burn both the alcohol and the fat brought to the liver, or is the lessened destruction of fat due wholly or in part to a lowered supply of carbohydrates necessary for the metabolism of the fats?

Such questions are beyond the scope of this article, obviously matters for experimentation. Removal of the liver from animals causes their death, and certainly its replacement by fat to the end that little normal liver tissue remains places such persons in jeopardy, and apparently may either alone cause death or constitute the main contributory factor.

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15. Pages, H.: Histoire d'un monton nügnard; enseignement qu'on tirer, Compt. rend. Soc. de biol. **4**:654-655, 1902.

16. Cited by Woodyatt, R. T.: The Clinical Use of Insulin, J. Metab. Res. **2**:800, 1922.

SUMMARY

The weight of the liver, when diseased, as well as the weight of other organs, has special significance when considered with regard to the weight of the body. With an extensive replacement of the liver by fat in persons who drink heavily of alcoholic beverages, death may be entirely unexpected and abrupt and with few symptoms of illness.

In postmortem examinations of such persons, little else than a large fatty liver may be found to explain death.

THE WILLIAM WOOD GERHARD GOLD MEDAL OF THE PHILADELPHIA PATHOLOGICAL SOCIETY

E. B. KRUMBHAAR, M.D., PH.D.
President of the Philadelphia Pathological Society
PHILADELPHIA

Since the foundation of the Philadelphia Pathological Society in 1857—one of the oldest, therefore, in this country—it has been an important influence in promoting the scientific study of medicine in this city and has, it is hoped, contributed its bit to the sum of knowledge concerning pathology. Even with the growth of the specialties it was able to maintain its position, deriving most of its support from scientifically minded clinicians in various branches, as well as from the smaller number of professional pathologists of the city's schools and hospitals. Endeavoring to interpret "pathology" in its broadest sense, the Society has been able to adapt itself to changing conditions, and has included in its programs reports of functional and chemical pathology and experimental work, as well as the more strictly morbid anatomic presentations.

Of late years, however, the emphasis that has been placed on some of the scientific branches closely related to pathology has resulted in many places in an almost overshadowing expansion of teaching staffs and material for publication, with the consequent development of special societies and journals in these lines. Much of the work thus produced is really pathology, and except for the forces indicated above might well have appeared in a pathologic milieu.

It was, therefore, with peculiar pleasure that the officers of our Society welcomed a suggestion that the Society establish a medal to be given as a reward for eminent work in pathology, in the hope that it might help to maintain the prestige of the subject and might stimulate additions to this branch of medical knowledge. In selecting a figure to honor, no one seemed more suitable than William Wood Gerhard, who was one of the most important contributors to the subject in this city, and who, as we learned later, had been the first president of the first pathologic society in this city, which antedated our own society by more than a decade, but which survived only a few years. Realization of the plan of offering such a medal was made possible by the generous offer of members of the Gerhard family to donate to the society a die, cut by the Medallic Art Company of New York from a design prepared by Dr. R. Tait McKenzie.

Fig. 1.—Obverse side of the William Wood Gerhard medal.

Fig. 2.—Reverse side of medal.

The medal is of 14 karat gold, 2 inches in diameter, bearing on the obverse the portrait of W. W. Gerhard in later life (obtained from a family photograph), his dates, 1809-1872, and McKenzie's monograph. On the reverse side, is an altar, such as is found on Greek coins of the best period, bearing the classic lamp of knowledge and entwined by a single snake of Aesculapius which gazes at the lamp. It bears the words, "The Philadelphia Pathological Society Honors Zeal in Research."

The first award was made on Nov. 12, 1925, in the Assembly room of the Pennsylvania Hospital to Dr. William H. Welch of Baltimore. This room, directly behind the celebrated picture of Christ healing the sick, by Benjamin West, was peculiarly suitable, as it was in the old "picture house" of the hospital that the Society was founded and held its earliest meetings. Dr. Welch's address (which was also the annual Gross Lecture of the Society) on "W. W. Gerhard and the Differentiation of Typhoid from Typhus Fever" was a delightful presentation of this complex subject. Besides giving many more biographic details of Gerhard than are available to the casual reader, he definitely fixed the great importance of Gerhard's contribution to the differentiation of the continued fevers, and molded a charming setting of the medical knowledge of the period.

It is hoped that the Society will be able to make future awards on suitable occasions (certainly not more often than once a year) for really eminent work in pathology—whether an outstanding original contribution or conspicuous service in advancing the subject in other ways. As there are no restrictions to the gift, the Society is free to make the award to investigators of any nationality or specialty. It is expected that they will customarily come to Philadelphia to receive the medal and deliver an address therefor, but on rare occasions the award will doubtless be made *in absentia*. The officers of the Society would be glad to receive suggestions of names of suitable candidates for the award, especially if accompanied by a statement of their qualifications.

Laboratory and Technical Notes

A CONTROL METHOD IN STAINING SMEARS FOR TUBERCLE BACILLI*

H. J. Corper, M.D., Denver

The clinical pathologist or practicing physician who is only occasionally called on to stain specimens of sputum, pus, urine, spinal fluid or other pathologic materials, fixed in smear, for tubercle bacilli, is frequently confronted with the feeling of uncertainty as to the infallibility of the method of staining and of the reagents used. Many times the stains and decolorizing agents have stood or a long time or may even have been made from unsuitable materials. Again, the details of staining the smear may be left to an assistant not particularly experienced in the manipulations, which, although apparently simple and with little obvious danger of error if properly performed, may give erroneous findings if the specimen is not properly fixed, the decolorizing carried too far or the actual staining not carried far enough. If tubercle bacilli are found in the preparation, little doubt or concern is experienced; but when the bacilli are not found, a feeling of uncertainty results. It is for this reason that a method of control should be welcome, especially to the physician who makes only an occasional examination for tubercle bacilli and to the clinical pathologist who wishes to place his technic on a reliable basis and give his diagnosis a stamp of authority. In the laboratory or sanatorium in which repeated specimens can be obtained and in which large numbers of smears are stained daily, this method might prove a burden and be unessential; but even here, when only a single specimen is available — as may be the case with spinal fluid or ureteral specimens of urine — a suitable control may serve a good purpose. As a result of an investigation of thirteen different staining methods for tubercle bacilli on smears,[1] it was found that when the technic is properly performed the majority of the methods may result in staining the tubercle bacilli with equal efficiency. There was, however, a decided difference in the ease of performance, speed and simplicity of the various individual methods. The finding of acid-fast bacilli (with the usual clinical and laboratory precautions) practically certifies a diagnosis of tuberculosis by the simple single stain methods, while in the Gram or double staining methods the presence of Gram granules alone requires corroborative positive animal inoculation findings to certify the diagnosis. It is for this reason that the Gram (Much) granules and combined methods are mainly of academic interest. Apparently the Gram granules do not differ from the granules seen in appropriately stained carbol-fuchsin preparations, since their numbers, morphology and location appear to be identical. For practical purposes, the simple steaming carbol-fuchsin (Ziehl-Neelson) method for staining tubercle bacilli, or one of its modifications, is

* From the Research Department, National Jewish Hospital for Consumptives, Denver.

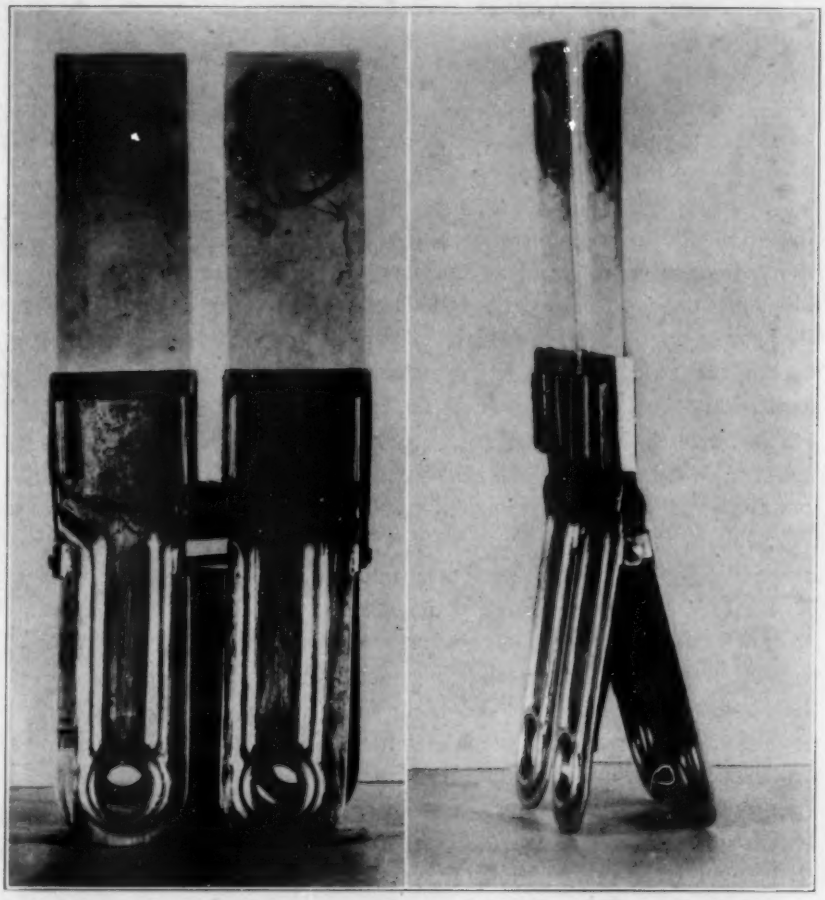
1. Corper, H. J.: Methods of Staining Tubercle Bacilli, to be published in the Journal of Laboratory and Clinical Medicine.

recommended to the clinical pathologist. The choice of colors remains with the individual worker, since any number of dye combinations can be used for staining and counter-staining tubercle bacilli. A negative finding by the simple method properly performed requires for further elaboration animal (guinea-pig) inoculation, because as many as a million bacilli (about 0.0001 mg.) per cubic centimeter of material is hardly discernible microscopically in the usual smears made, while from 10 to 100 bacilli from a culture freshly isolated from sputum suffices to infect a guinea-pig.

In order to insure the proper staining of the material to be examined under all circumstances, recourse must be had to the infallible method of the scientific investigator — a control test with the same materials and in the same manner. It would not do to compare an unknown specimen with a control from another material, since the thickness, consistency and composition of the material are all factors in determining staining, destaining and counterstaining. For the purpose of making a control, a suitable suspension of tubercle bacilli can be prepared so that 1 cc. contains about from 5 to 10 mg. of bacilli in 0.9 per cent. sodium chlorid solution and an equal part of pure acetone. The suspension is prepared by carefully grinding a weighed amount of the bacilli by means of a glass rod with rounded end slightly smaller than the bottom of a graduated centrifuge tube, first dry and then continuing after the drop by drop addition of the saline solution until one-half the total amount of solution has been added. A good uniform milky suspension, without lumps, should result, and then the other half of the total volume as pure acetone is slowly added with stirring during addition. This suspension keeps indefinitely and mixes well with water, sputum, serum and other body fluids in an amount of one part to ten of the specimen to be examined for tubercle bacilli. All that is necessary is to shake the bacillary suspension well before taking the requisite amount to be mixed with the material under examination. The suspension is best kept in a rubber stoppered receptacle to prevent evaporation of the liquid. The control material is prepared in a separate receptacle or test tube, and after complete and uniform mixing with the specimen a smear is carefully made at one end of an ordinary micro-slide, a similar smear being made on another slide with the original test specimen without the addition of bacilli. It is important in utilizing this method of control test to realize that contamination of the test specimen must be absolutely avoided by using separate utensils in making smears. It is well to bear in mind that tubercle bacilli retain their characteristic acid-fast properties even after drastic physical or chemical treatment, so that tubes, platinum loops, etc., must be thoroughly cleansed or completely burned off before being used again for another specimen. To facilitate and unify the staining of the control and test smears a special double slide clamp has proved serviceable. The clamp shown in the illustration[2] consists of two ordinary spring clamps attached to one solid frame, specially made to hold the narrow ends of two 3 by 1 inch standard micro-slides, and so constructed that the slides can be introduced individually but are held side by side so that in fixing, staining, washing, decolorizing and counterstaining the two smears — control and test — can be treated in an identical manner. Thus, if on microscopic examination the control reveals acid-fast bacilli, and the test slide, after careful search, reveals none, the

2. The double clamps used for control staining were made of nickel plated copper by K. A. Edstrom of the Denver Experimental Works, 2426 Humboldt Street, Denver.

negative report thus made, although it may not absolutely exclude the presence of tuberculosis, warrants injection into a guinea-pig and a consequent wait of from one to three months for final results, especially when only a single specimen is available. Concentration methods may be tried if sufficient material is at hand, but it is common laboratory experience that these methods do not appreciably increase the actual efficiency over the ordinary methods, which



Double slide clamp for staining.

seems logical when it is realized that the concentrate is not much beyond one-tenth the original volume and this merely means examining ten fields in the ordinary smear as compared to one with the concentrate. Concentration methods, with their necessarily complicated technic, introduce an additional danger of contamination of the specimen from outside sources and from unclean receptacles utilized in handing. The simpler the technic employed in examining for tubercle bacilli, the less is the danger of introducing errors in the findings.

General Review

RELATION OF ATOPIC HYPERSENSITIVENESS (HAY-FEVER, ASTHMA) TO ANAPHYLAXIS

A REVIEW OF RECENT LITERATURE *

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It is the purpose of this review to describe briefly the present state of knowledge concerning the more important aspects of the subject of hypersensitiveness, and to discuss the recent literature pertaining to them. In order to keep the review within the bounds naturally imposed by the character of this journal, I shall confine it to studies having some bearing on the conditions of hypersensitiveness affecting human beings, particularly the atopic form (asthma, hay-fever).

This task is difficult because nearly every question to be presented is in active controversy; indeed, it can be fairly said that there is little unanimity as to what is our "knowledge" of this important field of biologic and medical science.

In view of my participation in much of this controversy, and my personal identification with some of the views involved in it, my labor will be lightened by the adoption of a partisan attitude in the presentation.

The foremost difficulty that one meets in considering this subject is the almost hopelessly muddled state of the nomenclature, that is, the definition of the technical terms that have found their way into it. This confusion is not wholly the result of the differences of opinion just mentioned; in some instances, it seems rather to be due to an incomprehensibly arbitrary disregard of scientific precedent, in which I also unfortunately have offended. Much of the confusion would disappear if the scientifically established significance of the technical terms were always kept clearly in view.

Anaphylaxis.—This term for a long time was generally defined as a state of hypersensitiveness dependent on the presence of precipitin in certain tissues (chiefly muscular). However, Walzer and Grove,[1] in their recent experiments with guinea-pigs sensitized with pollen extracts,

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1. Walzer, M., and Grove, E. F.: J. Immunol. **10**:483, 1925.

failed to demonstrate precipitin, although the passive transfer of the sensitiveness was successful in their hands.

This experience with experimentally sensitized animals seems to afford some question as to the relation of precipitin to anaphylactic hypersensitiveness.

Moreover, a wide disproportion has been found between the precipitin content and the sensitizing power of different precipitating serums. Longcope [2] and Spain and Grove [3] have reported such a discrepancy in precipitating serums of rats, and in unpublished observations I have noted a similar discrepancy in precipitating serums of rabbits. Serums having a precipitating titer of 1:4,000, but almost lacking the power of passive sensitization, can be produced at will in rabbits. More impressive evidence against the identity of precipitin and anaphylactic antibody has been offered by Otto and Shirakawa (cited by Doerr), who have apparently separated these two functions out of an immune serum.

In view of this uncertainty of the relation of precipitin to anaphylactic sensitization, and because under unfavorable circumstances, such as dilution, the precipitation resulting from an immunologic reaction may be actually microscopic and therefore escape ordinary observation, it is obviously necessary to define anaphylaxis from another standpoint.

H. G. Wells [4] has done this in a most satisfactory manner by stating the criteria by which the anaphylactic condition is to be recognized. The criteria laid down by Wells are:

1. The observed toxicity of the injected material must depend on the sensitization of the animal; that is, the substance must not produce similar symptoms in nonsensitized animals.

2. The symptoms produced must be those characteristic of anaphylactic intoxication as observed in the usual reactions with typical soluble proteins, being therefore the same for all antigens with the same test animal, but differing characteristically with each species of animal.

3. It should be possible to demonstrate passive sensitization with the serum of sensitized animals.

4. It should be possible to demonstrate typical reactions in the virgin guinea-pig uterus strip.

5. It should be possible to demonstrate amelioration or prevention of the bronchial spasm in guinea-pigs by proper use of atropin and epinephrin.

6. The possibility that the observed symptoms are caused by capillary thrombosis or embolism must be excluded.

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2. Longcope, W. T.: J. Exper. Med. **36**:627, 1922.

3. Spain, W. C., and Grove, E. F.: J. Immunol. **10**:433, 1925.

4. Wells, H. G.: The Chemical Aspects of Immunity, The Chemical Catalog Company, Inc., New York, 1925.

7. After recovery from anaphylactic shock, a condition of desensitization should be exhibited under proper conditions.

Not all of these criteria can be considered essential. The fifth criterion, indeed, should be omitted, because in passively sensitized guinea-pigs, anaphylactic shock can often be produced with the intravenous injection of a minimal shocking dose of antigen with even a maximal dose of epinephrin (unpublished experiments by Grove and myself). A protective action of epinephrin could be observed in these experiments only in animals sensitized with a particular rabbit immune serum.

Two of the criteria offer means wherewith the hypersensitiveness of anaphylaxis may be distinguished from the other recognized forms. These are numbers 2 and 4.

Criterion 2 was used by me [5] in 1918 to separate from anaphylaxis the hypersensitiveness to tuberculin which is exhibited in all animals with similar symptoms that are different from the symptoms of the anaphylactic reaction in the respective animals.

It is obvious that, under criterion 3, Wells is thinking only of the principle of passive sensitization; he does not mean that anaphylactic hypersensitiveness is passively transferable from every actively sensitized animal.

Criterion 4 excludes atopic hypersensitiveness from anaphylaxis, as the atopic reagins are incapable of sensitizing the uterus of the guinea-pig.

ANAPHYLAXIS

Since this form of hypersensitiveness is the prototype by which the others have been studied, a brief space may be given to its consideration. Anaphylactic hypersensitiveness is an experimental condition in animals, resulting either from the parenteral administration of some antigens (active sensitization) and dependent on the production of antibodies in the animals, or from the transfer (passive sensitization) of the antibodies from a sensitive or "immune" animal to a normal one. This passive transfer can be effected artificially by injection, or naturally through the placenta or the milk from a sensitive mother.

There is practically no present disagreement as to the cellular site of the anaphylactic reaction. The antibody-antigen reactions that occur in the fluids of the body generally take place without any injurious consequences.

The site of the anaphylactic reaction, or "shock organ," as Doerr calls it, is different in the three animals in which this phenomenon has been most studied.

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5. Coca, A. F., in Tice: Practice of Medicine **1**:184, 1920.

In the guinea-pig, the outstanding anaphylactic symptoms of respiratory dyspnea are due to the antigen-antibody reaction that takes place in the bronchial smooth muscles, causing, in the latter, a tetanic contraction, often sufficient in power and duration to cause a physiologically complete interruption of respiration.

In the rabbit, after intravenous injection of the antigen, the most important anaphylactic symptom (circulatory dyspnea, with fall of arterial blood pressure) is due to the antigen-antibody reaction that occurs in the media of the pulmonary arterioles, causing an interruption of the lesser circulation. In the rabbit, the bronchial muscles are unaffected by the antigen-antibody reaction which is assumed to take place in them.

The anaphylactic arteriospasm of the rabbit was described by me [6] as an original observation in 1919. Manwaring, Marino and Beattie [7] were unable to demonstrate the phenomenon, and denied its existence. More recently, Drinker and Bronfenbrenner [8] made a careful analysis of it, and pointed out that it had been discovered in 1914 by Airila,[9] whose work had remained wholly unnoticed in the subsequent literature.

In the dog, the outstanding anaphylactic symptoms, whether acute or protracted, are due to the antigen-antibody reaction occurring in the liver, causing a congestion of that organ and in the tributaries of the portal vein sufficient to bring about a fatal lowering of the systemic blood pressure. In this animal, the antibody-antigen reaction that is assumed to take place in the bronchial muscles and media of the arterioles does so without producing any important physiologic effect.

ANTIANAPHYLAXIS (DESENSITIZATION, MASKED ANAPHYLAXIS)

The origin of the word antianaphylaxis has been briefly described in my recent elementary textbook.[10] In its original sense, it included the specific interference with the development of anaphylactic shock which ensues and persists for some time after the injection of a sublethal dose of antigen into an actively sensitized guinea-pig. By general consent, at the suggestion of Doerr, there was added to this effect the relative tolerance that can sometimes be effected with nonspecific agents—nonspecific antianaphylaxis.

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6. Coca, A. F.: J. Immunol. **4**:219, 1919.
7. Manwaring, W. H.; Marino, H. D., and Beattie, A. C.: Proc. Soc. Exper. Biol. & Med. **21**:202, 1923-1924.
8. Drinker, C. K., and Bronfenbrenner, J.: J. Immunol. **9**:387, 1924.
9. Airila, Y.: Skand. Arch. f. Physiol. **31**:388, 1914.
10. Coca, A. F.: Essentials of Immunology, Williams & Wilkins Company, Baltimore, 1925.

DESENSITIZATION

An analysis of the specific form of resistance to the anaphylactic shock just referred to has revealed two quite different mechanisms requiring special terms (desensitization and masked anaphylaxis).

The "resistance" of the early period following the injection of a sublethal quantity of antigen into a sensitized guinea-pig is due to a neutralization of the sensitizing antibodies. This effect is now generally designated as "desensitization." After the term "anaphylaxis," the word "desensitization" is perhaps the most generally misused one in the terminology of this subject. For example, one finds a recent paper by Karsner and Ecker [11] discussing "non-specific desensitization" in the human being, and another by Moldovan and Zolog [12] on the "desensitizing" action of India ink.

Furthermore, the tolerance induced in many subjects of hay-fever and asthma, by injections of the exciting agents, is universally spoken of as a "desensitization." Reference will presently be made to observations of Cooke and experiments by Levine and Coca which demonstrate the inapplicability of that term to such induced tolerance. There is, in fact, no demonstrable neutralization of the sensitizing bodies in the successful specific treatment of these two clinical forms of atopic hypersensitiveness.

MASKED ANAPHYLAXIS

This is the happily chosen expression offered by Doerr [13] to designate the condition of relative resistance to anaphylactic shock exhibited by actively sensitized animals that have received one or more further injections of the antigen at proper intervals.

The state of "masked anaphylaxis" in such animals is most clearly revealed in the perfusion experiments of Manwaring and Kusama.[14] These investigators perfused the lungs of such "immune" guinea-pigs with saline solution, and found those organs more sensitive to the antigen than the lungs of ordinarily sensitized animals. When, however, the serum of the "immune" animals was mixed with the perfusion fluid, the lungs were found to be less sensitive to (protected against) the antigen, apparently on account of the antibodies contained in the immune serum.

The earlier experiments of Weil, in which the actively sensitized guinea-pig was "protected" with a large dose of immune rabbit's serum intravenously injected, have been shown to be inadequate in explana-

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11. Karsner, H. T., and Ecker, E. E.: J. Infect. Dis. **5**:71, 1922.
12. Moldovan, I., and Zolog, M.: Compt. rend. Soc. de biol. **92**:720, 1925.
13. Doerr, R.: Ergebn. d. Hyg., Bakteriol., Immunitätsf. **5**:71, 1922.
14. Manwaring, W. H., and Kusama, Y.: J. Immunol. **2**:157, 1917.

tion of "masked anaphylaxis," since later investigators obtained nearly the same protection with normal rabbit's serum.[15]

Wells wishes to change the historically established significance of the term antianaphylaxis to make it apply only to the "protection" of the sensitive tissues of the anaphylactic animal by circulating antibodies presumably demonstrated by the experiment of Manwaring and Kusama.

INFLUENCE OF HEREDITY IN ANAPHYLAXIS

Anaphylactic hypersensitiveness, being an acquired state, is not inheritable. It can be transmitted from sensitive mother to offspring through the placenta or the milk, as a kind of passive transference, but not from a sensitive male parent.

Some recent observation of Lewis and Loomis on guinea-pigs indicate that the faculty of becoming sensitive is a constitutional one, which is subject to the influence of heredity. These observations will be discussed later.

In rabbits also, as is no doubt generally known, the faculty of becoming sensitized under identical treatment is exhibited in widely different degree in the different individuals, and it seems reasonable to suppose that these differences are in some way controlled by heredity.

ALLERGY

After the phenomenon of anaphylactic sensitiveness had been discovered and understood, it became necessary to consider a term that would embrace all phenomena related to anaphylaxis, and here we were led into an error of terminology, which, no doubt, will pester the science of immunology for some time to come. Pirquet coined the word "allergie," and Doerr adopted it in its strictly etymologic sense of "altered reactivity" as an inclusive heading for anaphylactic sensitiveness and allied conditions. The logical outcome of this has been the necessity of referring to immunity to diphtheria as an allergic state; also the nonspecific morphine tolerance must be called allergy. However, the student of hypersensitivness in its immunologic sense has hardly a remote interest in either of these two wholly unrelated phenomena, which might warrant their inclusion in any useful classification of hypersensitive conditions. No fundamental principle has been advanced that is important enough to justify such an association.

The term allergy is still being used, but generally without consideration of its full significance.

Wells (in a personal communication) accepts Doerr's definition of allergy in somewhat modified form as "altered reactivity on an

15. Friedberger and Hjelt, cited by Doerr, Thomsen, O.: Ztschr. f. Immunitätsf. **26**:251, 1917.

immunological basis," which, of course, covers antitoxin immunity (diphtheria, tetanus, etc.) as well as anaphylaxis.

Zinsser, while recognizing its etymology, actually applies it in nearly the sense that I proposed for it in 1918 [5]—"hypersensitiveness not known to be mediated by antibodies."

Karsner and Ecker [16] do not mention the word.

Duke [17] defends the word, without stating whether he considers that an individual immune to diphtheria, that is, exhibiting an "altered reactivity" to diphtheria toxin, is allergic.

Lewis and Loomis [18] frankly disregard the prior definition laid down by Doerr, and offer the following: "Allergic irritability" is "a general characteristic of the animal on the basis of which it reacts to stimuli of the antigenic class, whether they be helpful, injurious or indifferent to bodily health."

Longcope, likewise, rejects the definition of Doerr, expressing his view (in a personal communication) as follows:

> I rather think of allergy as defining the altered reactivity of the tissues which occurs in man and animals following artificial sensitization to a foreign protein which, upon first injection, is relatively innocuous, or to a similar state of hypersensitiveness which occurs spontaneously in certain individuals; or finally to a state of specific altered reactivity of the tissues to products of bacterial growth or disintegration during the course or following an infection by the bacteria. The same condition occurs during the infection from certain viruses of unknown origin and infestation by animal parasites.

It is seen that the meaning of the word "allergy," as interpreted by Longcope, is distinguishable from the immunologic significance of the term "hypersensitiveness," while, in the sense of Lewis and Loomis, the word allergy practically excludes the entire category that Zinsser has in mind under it.

In view of this complete want of agreement as to the meaning of the term, it must be looked on as lacking scientific standing as well as any practical usefulness.

My efforts to emphasize, by means of classification, the similarities and also the differences in the several forms of hypersensitiveness, have met with objections on every hand; objections, it should be pointed out, that in some part are grounded on misunderstanding of my statements.

Doerr,[19] for example, writes "Der Mensch kann also nach Coca überhaupt nicht willkürlich sensibilisiert werden . . ." a statement which cannot be found in my publications.

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16. Karsner, H. T., and Ecker, E. E.: Principles of Immunology, Philadelphia, J. B. Lippincott Company, 1921.

17. Duke, W. W.: Asthma, Hay Fever, etc., St. Louis, C. V. Mosby Company, 1925.

18. Lewis, P. A., and Loomis, D.: J. Exper. Med. **40**:503, 1924.

19. Doerr, R.: Ergebn. d. Hyg., Bakteriol., Immunitätsf. **5**:97, 1922.

Zinsser [20] writes, ". . . our own opinion (does not) necessarily agree with the assumption that there is absolutely no connection between protein hypersusceptibility and other forms, as maintained by Coca." I cannot recall having maintained such an uninviting notion.

Wells [21] says:

> Although Coca and others have suggested various modifications of the terminology used in discussing these processes of altered sensitivity, it is agreed by many writers that the term anaphylaxis should be restricted to the condition of hypersensitivity to definitely antigenic substances, according to the limitations specified above.

I have always entertained this view of the term anaphylaxis and I have expressed it rather prominently in several publications.

The classification referred to is

HYPERSENSITIVENESS

Normal (Cooke)	Abnormal
Dermatitis venenata	Anaphylaxis
Serum disease	Hypersensitiveness of infection
	Atopy

Zinsser [22] fears that such a classification may "influence investigators to overlook fundamental similarities" in these different forms. It may be true that the similarity among them is less conspicuous than are the differences. However, the important similarity is amply recognized, not only in their association under one heading, but also in the definition of that comprehensive term, which follows.

Hypersensitiveness, in its immunologic sense, is a sensitiveness in man and lower animal that is mediated by a special mechanism. This idea may be expressed also in the following way: In immunologic hypersensitiveness, the exciting agent—usually an antigen—is not by itself irritating to the susceptible tissues. It causes the irritation only in conjunction with another body to which, so far as our knowledge extends, it is specifically related. The related body in anaphylactic hypersensitiveness is an antibody.

In this definition of hypersensitiveness which I laid down in conference with Cooke,[23] it is seen that a special reacting body is assumed to exist as an essential cause of each form of this phenomenon. The assumption conveys the expectation that, in every such instance, a specifically reacting antibody or antibody-like substance may be discovered.

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20. Zinsser, H.: Infection and Resistance, Ed. 3, 1925, p. 411.
21. Wells, H. G.: Footnote 4, p. 200.
22. Zinsser, H.: Footnote 20, p. 518.
23. Coca, A. F., and Cooke, R. A.: J. Immunol. **8**:163, 1923.

There seems to be a general impression, although this is not always explicitly stated by writers on this subject, that any physiological reaction which can be shown to be due to the interaction of antigen and its antibody or antibody-like substance is to be identified, in this fact alone, as an anaphylactic phenomenon.[24]

However, this would be as reasonable as if one should wish, merely on the ground of a single common character, to call every dog a "dachshund" or every bird a parrot. The differences among the several forms of hypersensitiveness are as clear and as important as those among the races of dogs or varieties of birds.

It should be reiterated, as often as necessary, that, if progress is to be made in the study of these various phenomena of hypersensitiveness, one must hold to a clear definition of the anaphylactic form such as that presented in the "criteria" of Wells.

Any definition of this key term that would leave in full view the differences between this and the other forms of hypersensitiveness would answer the purpose; that provided by Wells' criteria seems the best yet offered.

To summarize the present state of the controversy as to the classification of the phenomena under consideration, one may say that one side is making an effort to minimize the differences among the different forms of hypersensitiveness, although their individual identities are recognized, while the other side is being charged with overlooking the similarities presented by the different forms, although the essential similarity of all of them is clearly stated in the definition of the inclusive term.

The classification given above has had the result of formally separating two forms of hypersensitiveness from the others. This was accomplished by the simple introduction of two new terms; namely, "hypersensitiveness of infection" (tuberculin-mallein type) and "atopy" (the inherited form including hay-fever, bronchial asthma and others not yet determined). This separation has not only drawn particular attention to the several important differences that characterize these and the remaining forms and has provided convenient means of designating them, but it has, as Krumwiede [25] remarks, served a practical end in counteracting the widespread false impression in the medical pro-

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24. Doerr, for example, writes "Dürfen wir nun die Idiosynkrasien gegen Antigene auf Grund des in einigen Fällen erbrachten Nachweises spezifischer Antikörper als Antigen-Antikörper-Reaktionen ansehen? Dürfen wir sie mit den anaphylaktischen Prozessen identifizieren?" (Ergebn. d. Hyg., Bakteriol., Immunitätsf. **5**:85, 1922.)

25. Park, W. H.; Williams, A., and Krumwiede, C.: The Pathogenic Microorganisms, Ed. 8, 1924, p. 236.

fession that all of the principles of anaphylactic hypersensitiveness are directly applicable to the several forms of hypersensitiveness encountered in human beings.

ATOPY

The opposition to the aforementioned classifications has centered mainly on my separation of hay-fever, asthma and allied conditions (atopy) from anaphylactic hypersensitiveness. This separation was made at first because of: (1) the usual absence of demonstrable precipitin in the blood of atopic individuals; (2) the supposed nonantigenic nature of some of the atopens among which the pollens were considered; (3) the strongly familial character of atopy; (4) the reported instances of atopic sensitiveness having developed supposedly without previous contact with the exciting agent, this being taken to indicate a purely physiologic origin of the sensitiveness independent of any immunologic stimulus; (5) the absence of the characteristic phenomenon of desensitization in these conditions. The force of all of these points, one by one, has been nullified or modified by subsequent investigations.

Precipitin has still not been shown to be implicated in the causation of atopic hypersensitiveness; however, another reacting body has been discovered, through the ingenious experiment of Prausnitz and Küstner.[26] These investigators demonstrated the existence of a specific sensitizing property in the blood serum of a fish-sensitive person (Küstner) by the local passive sensitization of the skin of a person not sensitive to fish (Prausnitz). The passive sensitization was effected by intradermal injection of the atopic serum. This important observation was confirmed by de Besche,[27] and more recently, it has been extensively studied in this institution.

Coca and Grove[28] have suggested the term "atopic reagin" to designate the sensitizing bodies demonstrable in atopic hypersensitiveness with the technic of Prausnitz and Küstner. This suggestion was drawn from the belief of these writers that the sensitizing bodies in atopic hypersensitiveness are different from the ordinary antibodies, and because at the time the suggestion was made there was no available evidence that the reagins are produced under antigenic stimulation.

The main difference noted by Coca and Grove between the atopic reagins and the typical anaphylactic antibodies lay in the fact that with the former bodies several repeated reactions can be elicited with identical quantities of the related atopen, whereas, with the latter bodies (accord-

26. Prausnitz, C., and Küstner, H.: Zentralbl. f. Bakteriol., Pt. 1, Orig. **86**: 160, 1921.

27. De Besche, A.: Am. J. M. Sc. **166**:265, 1923.

28. Coca, A. F., and Grove, E. F.: J. Immunol. **10**:445, 1925.

ing to Coca and Kosakai,[29] confirmed by Walzer and Grove,[1] with the Dale technic) a second reaction can be produced only with a multiple of the first dose.

The observation of this peculiarity of the atopic reagins has been thoroughly confirmed by Levine and Coca,[30] also by Walzer, in some unpublished experiments.

An exception to the rule of Coca and Kosakai seems to be presented in the observation of Walzer and Grove that pollen sensitive uteri sometimes respond with two distinct reactions to the same concentration of the pollen extract (the bath of Dale-Ringer solution having been changed between the two tests).

This exception has, perhaps, the same cause as the absence of visible precipitation, namely, the special nature of the pollen antigen, which has been shown [31] not to be the protein of the pollen, but a relatively indigestible substance not accessible to chemical analysis. The antibodies presumably are produced by the same immunologic organ as are the antiprotein sensitizing bodies in ordinary anaphylaxis, and are probably of the same nature. The exception described above should not be set at once on a level with the repeated reactions obtained with the atopic regions, because in the latter case it is immaterial whether the atopen is the pollen antigen or an antigenic protein in rabbit epithelium. Hence, the peculiarity of the repeated reactivity is here a property of the reagin.

Another peculiarity of the atopic reagin found by Levine and Coca [30] is its complete inability to affect the activity of its related atopen when mixed with the latter in the test tube. Coca and Grove [28] had reported that the sensitizing power of the reagin can be entirely suppressed with a suitable quantity of the atopen; but Levine and Coca have shown that the activity of the latter in such mixtures is wholly unaffected by the presence of the reagin. This fact has no analog in immunology. It would seem to present a difficulty for Doerr's [32] second requirement regarding the interaction of antigen and antibody.

I have considered the possibility that the atopic reagins are not antibodies which are produced under antigenic stimulation, but physiologic elements produced without such stimulation, as is the case with the human isohemagglutinins.

However, some experiments by Levine and Coca, to be published, seem to show that the reagin content of the blood is distinctly (two to four times) increased after therapeutic injection of the exciting agent —pollen extract.

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29. Coca, A. F., and Kosakai, M.: J. Immunol. **5**:297, 1920.
30. Levine, P., and Coca, A. F.: J. Immunol., to be published.
31. Grove, E. F., and Coca, A. F.: J. Immunol. **10**:471, 1925.
32. Doerr, R.: Die Naturwissenschaften **12**:1029, 1924.

If this observation is confirmed, it will indicate that the reagin is an antibody. This conclusion is strengthened by the finding of Coca and Grove that reagins are not demonstrable in individuals sensitive only to a nonantigenic substance (quinin, mercury, aspirin), though the finding leaves unsolved the mystery of the hypersensitiveness to these and other nonantigenic "drugs."

The conclusion that the atopic reagin is an antibody seems to make necessary the assumption of two immunologic organs in human beings, namely, the precipitinogenic organ and the reaginogenic organ.

Normal (nonatopic) human beings produce, under the antigenic stimulation of horse serum (for example), a precipitating serum against this foreign protein, with which it is possible to sensitize the uterus of the guinea-pig.

Atopic individuals, on the other hand, while not necessarily lacking the power of precipitin production, are always capable of producing another antibody, which is unable to sensitize the uterus of the guinea-pig, but is able to sensitize the normal receptive human skin. Rabbit precipitin is incapable of sensitizing the human skin.[28]

The atopic reaginogenic organ or function is subject strictly to the familial influence that was demonstrated by Cooke and Vander Veer,[33] and studied further by Spain and Cooke.

The faculty of nonatopic human subjects to produce precipitin has been studied recently by Schloss [34] and his co-workers. These investigators had found anticow's milk precipitin and a distinct power of passive sensitization in the blood of marantic babies fed on cow's milk. When egg white was added to the food, the production of anti-egg-white precipitin promptly followed (within a few weeks). The same results were obtained on feeding with sheep's serum and the globulin of almond.

As has been indicated, none of these babies presented any clinical signs of atopic hypersensitiveness.

More recently, these authors [35] have discovered precipitin in normal infants, indicating a permeability of the normal gastro-intestinal mucosa to undigested foreign protein.

Dr. Schloss states (personal communication) that in from 50 to 60 per cent of both the marantic and the "normal" babies, a positive skin reaction to the foreign proteins used could be elicited. However, in the majority of these cases, the cutaneous sensitiveness disappeared after a time.

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33. Cooke, R. A., and Vander Veer, A.: J. Immunol. **1**:201, 1916.
34. Anderson, A. F., and Schloss, O. M.: J. Dis. Child. **26**:451, 1923.
35. Dubois, R.; Schloss, O. M., and Anderson, A. F.: To be published.

This phenomenon of gastro-intestinal permeability is being studied by Walzer in the New York Hospital with a wholly different method. Walzer sensitizes the skin of normal individuals with the passive method of Prausnitz and Küstner, described above, to some edible protein, such as egg-white or fish. The individual then ingests some of the related atopen, and, within from three minutes to an hour, or longer, a wheal with a zone of erythema develops in the passively sensitized site. This phenomenon could not be elicited by Walzer with all atopic serums that were capable of sensitizing the normal skin to the local cutaneous test. The experiment has been successful so far with only two such serums.

There is a general impression among the medical profession that a second administration of a foreign protein is necessarily dangerous, especially if an alteration of the skin reactivity has occurred (Hooker)[36] or if precipitin is demonstrable in the blood (Anderson and Schloss).[34] A direct experiment in the latter situation has not been reported. However, the observations of Park[37] should set at rest any apprehension in the former case.

In the period preceding the introduction of precautionary cutaneous tests, Park had given second intravenous injections of antitoxic serum into a number of individuals. When Hooker was making his report on the development of cutaneous reactivity after the administration of even small quantities of horse serum, Park recalled his earlier unpublished observations, and, with this assurance of a negative result, he gave second injections of horse serum intravenously into several individuals whose cutaneous reactivity had changed from negative to marked positive (confirming Hooker). None of these individuals, however, suffered the slightest constitutional reaction as a result of the second injection.

The significance of the demonstration of precipitin in hypersensitive human subjects has been illuminated finally by the discovery of the atopic reagins and by the researches of Schloss and his co-workers referred to in the foregoing. It must seem surprising, in retrospect, even to the most confirmed adherent of the anaphylactic nature of human hypersensitiveness, that any importance should have been attached to the finding of precipitin in hypersensitive human subjects.[5] Such findings merely show that precipitin and reagin can both be present in the blood of the human subject.

The astonishing permeability of the normal intestinal wall for foreign protein that has been demonstrated by Schloss and Walzer, and the ready production of ordinary anaphylactic antibodies in non-

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36. Hooker, S. B.: J. Immunol. **9**:7, 1924.
37. Park, W. H.: Personal communication.

sensitive human subjects, which has been so amply demonstrated by the former author, constitutes important evidence in the illumination of Doerr's [38] conception of the anaphylactic nature of "idiosyncrasy." Doerr cites reports by Ancona [39] in Italy to the effect that contact with the dust of a certain spoiled, infested grain causes skin eruption and asthma, sooner or later, in all human subjects, and he uses this in support of his idea that the development of idiosyncrasy in human beings depends on a relative ability of the individual to produce antibodies. Anderson and Schloss have shown that nonsensitive human subjects may have a considerable power of production of anaphylactic antibodies, whereas the blood of naturally sensitive (atopic) human subjects may lack such antibodies completely. Certainly, these observers, as well as Walzer, have provided ample evidence of a constant parenteral contact with unaltered proteins on the part of many nonsensitive human beings.

I would point out, furthermore, that daily contact, by inhalation on the part of pollen collectors during several pollenation seasons, with relatively enormous quantities of fresh pollen, has not resulted in a single case of hay-fever among more than fifty of these persons in my acquaintance. Yet the relatively high incidence of pollen sensitiveness among atopic individuals indicates a correspondingly high "antigenic" property in individuals of atopic lineage. Of the 439 atopic individuals taken at random for study by Spain and Cooke,[40] 206 were sensitive to ragweed pollen.

Perhaps some caution is advisable in the interpretation of Ancona's observation. A more detailed report may be awaited before one accepts the general statement that "practically all" individuals that remain "long enough" in contact with the grain infested with the larvae of *Pediculoides ventricosus* develop asthma. Furthermore, the nature of this acquired hypersensitiveness must be studied with the use of the method of passive transfer of Prausnitz and Küstner. The high incidence of dermatitis among affected individuals suggests a relationship to dermatitis venenata in which passive transfer has thus far failed.

One should not deny the possibility, urged by Doerr, that there is no sharp line of separation between atopic and nonatopic human beings, as the reports of Ancona would seem to indicate. However, this theoretical possibility is by no means sufficient to erase the practical fact of the identity of the atopic group of human hypersensitiveness.

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38. Doerr, R.: Vortrag, gehalten in der Sitzung der Medizinischen Hauptgruppe der 88 Versammlung Deutscher Naturforscher und Aerzte in Innsbruck vom 21 bis 27 September, 1924.

39. Ancona, G.: Sperimentale **76**:270, 1922.

40. Spain, W. C., and Cooke, R. A.: J. Immunol. **9**:521, 1924.

Where else in biology, one may ask, are to be found the sharp lines of separation required by Doerr?

In 1916, Cooke and Vander Veer [33] published observations showing that atopic individuals are no more prone to become sensitive to horse serum (administered by subcutaneous injection) than are nonatopic individuals. Against this conclusion, Doerr [32] cites the well-known fact reported by Bloch and by Storm van Leeuwen that the skin of atopic individuals reacts to various proteins more frequently than does the skin of nonatopic subjects. Doerr seems to recognize the nonatopic nature of these skin reactions by remarking that they render diagnosis difficult, but from his designation of them as "nebenallergien" he seems to look on them as indicating only lesser degrees of "idiosyncrasy." However, Coca and Grove [28] and Walzer have found the blood quite lacking in reagins for the materials causing these "nonspecific" reactions. The significance of the reactions, as indicated by these observations, makes them unavailable for Doerr's argument against the conclusions of Cooke and Vander Veer. Such reactions may be classed with those described by Hooker and by Park as developing after injections of foreign serum.

NONANTIGENIC ATOPENS

The question has not yet been definitely answered whether the so-called drug idiosyncrasy is an exhibition of atopic hypersensitiveness; in other words, it has not been conclusively proved that drug idiosyncrasy (which it seems to me could conveniently be taken to mean the human hypersensitiveness to nonantigenic substances) is subject to the atopic familial influence.

Drug idiosyncrasy occurs in a relatively small percentage of the members of atopic families. Cooke and Vander Veer and Spain and Cooke mention only ten instances among the 1,000 atopic individuals and the numerous relatives of those individuals studied by them.

While one is tempted to anticipate the actual demonstration of the atopic nature of drug idionsyncrasy, there is an outstanding peculiarity of this category of hypersensitiveness which seems to invite caution before such a conclusion; this peculiarity is the absence of demonstrable reagins in the blood of the affected individuals.[28]

On the other hand, one can consider this peculiarity from an opposite point of view.

In fact, one can look on the reagins as an unessential accompaniment to the atopic hypersensitiveness to antigenic substances; in this point of view may be found, perhaps, an explanation of the otherwise inexplicable findings of Levine and myself,[30] which will be discussed presently. Certainly the evident lack of relationship between the severity of the clinical symptoms of atopy and the blood content of

atopic reagins speaks for the greater importance of the "tissue factor" as compared with the reagins.

There are a number of atopic excitants whose anaphylactogenic properties are demonstrated with distinctly greater difficulty than is the case with the usual proteins. Among these is the pollen atopen. Until recently it was assumed that the pollen atopen is the pollen protein; however, the experiments of Grove [31] and myself have shown that this is not the case, because, after all detectable protein nitrogen has been removed from pollen extracts by tryptic digestion and dialysis, the specific activity of the fluid remains the same as that of the untreated extract. It is not possible to state definitely that the pollen atopen is not a protein; one can only say that it is not the ordinary, easily digestible protein of pollen. It may be classified, for the present, with such chemically inaccessible substances as enzymes and toxins. The experiments just mentioned showed, furthermore, that the atopens of house dust and orris root are of a nature similar to that of pollen. The atopens of horse dander and of green pea, on the contrary, were shown to be digestible proteins.

As has been indicated in the foregoing, my assumption that the pollen atopen is nonantigenic has finally been refuted by Walzer and Grove.[1] Koessler has reported successful sensitization of guinea-pigs with pollen extracts, and Parker [41] described the active sensitization of the uterine muscle of the guinea-pig with pollen extracts. These results did not identify the anaphylactogen as the atopen. However, Walzer and Grove were able to show that the protein-free pollen extract, in which the pollen atopen was quantitatively preserved, contained an anaphylactogenic substance presumably identical with the atopic excitant.

The experiments of Alexander [42] on the anaphylactogenic properties of rye pollen were not made in a manner to identify the anaphylactogen in that pollen with the atopic excitant.

The recent demonstration by Parker [43] of a precipitinogenic substance in pollen extract is, like the results with the anaphylaxis technic, without significance as to the nature of the pollen atopen. Mrs. Parker reports her impression that the precipitin, which she produced against giant ragweed pollen, was specific for that particular pollen; however, the serum which she allowed me to test reacted at least as well with the extract of the low ragweed pollen as with that of the giant ragweed pollen. When tested with the digested and dialyzed pollen extract, the precipitation was distinctly less than with the untreated extract, giving the impression that the precipitin was related to the digestible

41. Parker, Julia T.: Proc. Soc. Exper. Biol. & Med. **18**:237, 1921.
42. Alexander, M. E.: J. Immunol. **8**:457, 1923.
43. Parker, J. T.: J. Immunol. **9**:515, 1924.

protein in the extract, to which the human subject presumably does not become sensitive.

The study of the relations of different atopens has been continued with the use of the anaphylactic experiment. In 1917, Flood,[44] in association with Cooke and Coca, sensitized guinea-pigs with an extract of horse dander, and showed a specific difference between the anaphylactogens of that material and those of horse serum. Recently, Friedberger and Kamio [45] reported failure to sensitize guinea-pigs to the extract of horse dander. Longcope, O'Brien and Perlzweig,[46] however, have confirmed the results of Flood in every particular, extending the experiments with the use of Dale's technic.

These observations possess a biologic interest without, however, necessarily throwing light on the nature of the atopens of the two materials used. That this is true can be demonstrated in some unpublished experiments by Grove and myself. The serum of an asthmatic person sensitive to horse dander extract and to horse serum was injected intradermally into nonsensitive persons. The sensitized sites were found to be sensitive to the horse dander extract and the horse serum. After one such skin site had been desensitized with two injections of the dander extract, it was found to be completely insensitive also to the horse serum.

This finding need not be interpreted as proving a complete identity of the atopens of the two materials—further study of this question is required; however, it does demonstrate an identity of one atopic excitant in both of them.

In a brief report just published without protocols, Ratner, Jackson, and Gruehl [47] state that they have obtained "cross anaphylactic relationship" between dander and serum. In view of the previous concordant results just described, judgment regarding the statements of Ratner, Jackson and Gruehl may be suspended until access is obtained to the details of their experiments. The statement of these authors that their results depended in part on their "not relying on the Dale method as a final criterion for anaphylaxis" may perhaps be judged in the light of the painstaking experiments of Walzer and Grove who showed that, as a final criterion for anaphylaxis, the Dale method presents distinct advantages over the criterion of general shock in the guinea-pig.

That the nonatopic cutaneous sensitiveness to horse serum may be exhibited to more than one of the component serum proteins has been

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44. Cooke, R. A.; Flood, E. P., and Coca, A. F.: J. Immunol. **2**:217, 1917.

45. Friedberger, E., and Kamio, T.: Ztschr. f. Immunitätsf. **37**:379, 1923.

46. Longcope, W. T.; O'Brien, D. P., and Perlzweig, W. A.: J. Immunol. **10**:599, 1925.

47. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Proc. Soc. Exper. Biol. & Med. **23**:16, 1925.

well demonstrated by Hooker.[48] In an individual, in whom a cutaneous sensitivity had developed as a result of a previous injection of horse serum, the intradermal injection of this material caused three successive reactions, at intervals of thirty minutes, five hours and twelve hours, respectively. When the individual was tested with the pseudoglobulin, euglobulin, and albumin isolated from horse serum, the reactions with these three materials developed after 60 minutes, five hours and seven hours, respectively.

SIGNIFICANCE OF THE FAMILIAL CHARACTER OF ATOPY

If there was any reasonable ground for the doubt expressed by Doerr [32] as to the cogency of the evidence presented by Cooke and Vander Veer [33] regarding the familial nature of atopic hypersensitiveness, this uncertainty would seem to have been made unnecessary by the recent important publication by Spain and Cooke.[40] Spain and Cooke have done somewhat more than confirm the findings of Cooke and Vander Veer. They have been able to improve the agreement between the percentages of affected offspring found and those expected under the mendelian rule. The discrepancy of the percentages under a bilateral familial influence (too small) and those under a unilateral influence (too great) may be susceptible of the same explanation. On the one hand, some of the children of the first group possessed the atopic tendency without having been placed in circumstances in which it could be exhibited; while, on the other hand, some of the negative lines among the second group may have carried the atopic character without exhibiting it, or without its having been elicited in the history.

Adkinson [49] made a statistical study similar to that of Cooke and Vander Veer, but reached the conclusion that the familial factor is recessive. This hypothesis, according to Spain and Cooke, has no support in the percentage of the affected offspring of two affected parents, which is 71. If the factor were recessive, all such offspring should be affected.

Lewis and Loomis [25] report that inbred lines of guinea-pigs which have previously been observed to differ in their susceptibility to tuberculosis, differ in their anaphylactic responses as well. The families that are relatively resistant to tuberculosis appear also to be somewhat more resistant to one or more of the phases of the anaphylactic reaction complex. These authors say that their "experiments seem to have a direct bearing on the questions arising from the conception that asthma depends on an anaphylactic phenomenon and that the tendency to asthma is inherited."

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48. Hooker, S. B.: J. Immunol. **8**:469, 1923.
49. Adkinson, J.: Genetics **5**:363, 1920.

Indeed, one is inclined to agree with this conclusion, but with certain reservations. In order to duplicate the familial influence that is so clearly evident in atopy, one should be able to breed out a family of guinea-pigs (or other animal susceptible of anaphylactic sensitization) which could not be sensitized with any protein.[50] Also, one should at the same time present some explanation of the fact that the sensitiveness of so many atopic human beings is limited to only one or two substances. This peculiarity of atopy has not yet been duplicated in lower animals, although it is known that certain horses yield antitoxin to one toxin more readily than to another (Park; personal communication).

In his argument against the importance that has been ascribed by the writer to the familial factor in atopy, Doerr urges attention to the many instances of acquired sensitiveness in human beings to proteins, and, I would add, to nonantigenic chemicals (arsenic) as well.

Here also one is in some danger of mistaking shadow for substance. Some of the observations cited by Doerr, those of Park [37] mentioned in the foregoing, showed that the experimentally "induced" sensitiveness of human beings is easily distinguishable from the atopic form in its typical expressions. The intravenous injection of horse serum into such "sensitized" individuals produced, in Park's hands, not the slightest symptoms. It remains to be seen whether, in such individuals, blood-borne reagins are demonstrable.

DEVELOPMENT OF ATOPIC HYPERSENSITIVENESS WITHOUT PREVIOUS CONTACT WITH EXCITANT

There are no recent observations confirming the isolated ones of Dunbar and Cooke [44] which seem to show that atopic hypersensitiveness may exist without previous contact with the excitant. Grove and I [28] tested a number of hay-fever subjects with the pollen of *Algeroba* obtained from Hawaii, and in several of these we obtained marked cutaneous reactions. However, since the passive transfer of such sensitiveness failed in every instance, the reactions were considered nonspecific.

The result of study by Grove and myself on the relation of the atopens of horse dander and of horse serum has a theoretical significance in relation to the question under discussion. If, as was not the case in that study, atopic sensitiveness could be demonstrated to a component of horse serum that is not present in horse dander, such an

50. Here one may consider again Doerr's reliance on Ancona's observations of those having to do with a certain spoiled grain as proving that all human beings possess a greater or less faculty of becoming "sensitized." This point is discussed on page 109.

observation would provide presumptive evidence that previous contact with the atopen is not essential to the development of atopic hypersensitiveness.

The difficulty in any given instance of proving the complete absence of previous contact with an atopic excitant and the small number of instances thus far reported of an "attack" occurring on a supposed first contact should make such evidence of questionable value.

DESENSITIZATION IN ATOPY

Cooke observed that successful specific treatment of atopic conditions (hay-fever, asthma) produces no noticeable diminution in the degree of sensitiveness of the skin or conjunctiva. This observation has found confirmation in a recent quantitative study of the reagins in ante-treatment and post-treatment blood of subjects with hay-fever by Levine and myself.[30] In no case could the injection be shown to lower the reagin content of the blood. These results do not allow one to speak of the protective effect of the specific treatment of atopy as a "desensitization."

These findings have a direct bearing on the experiments published by Mackenzie and Baldwin [51] as showing a local desensitization in atopic hypersensitiveness.

Cooke's subsequent experiments indicated that Mackenzie's conclusions were untenable, and the findings just mentioned add complete confirmation to Cooke's results.

While all efforts to demonstrate desensitization in an atopic individual have failed, one should admit the principle of desensitization as demonstrated in the normal human skin passively sensitized with the atopic reagins, that is, under the "proper conditions" of Wells' seventh criterion.

SUMMARY

As has been stated, the force of all of the arguments on which the separation of atopy and anaphylaxis was originally made has been nullified or modified. However, the modifications which have been dictated by the newly acquired experimental facts have left the proposed separaiton, if anything, more securely founded.

In addition to the merely negative argument of lacking precipitin in atopic hypersensitiveness, there is now the positive fact of a "special mechanism," the atopic reagin, which differs from the anaphylactic antibody in three important respects: its property of causing repeated physiologic reactions on repeated contact with identical quantities of the related protein atopen, its complete inability to "neutralize" that

51. Mackenzie, G. M., and Baldwin, L. B.: Proc. Soc. Exper. Biol. & Med. **18**:214, 1921; Arch. Int. Med. **28**:722, 1921.

atopen, and its inability to sensitize the uterus of the guinea-pig. To these differences in the properties of the two mechanisms must be added the further important differentiating consideration that if, as it seems possible, the atopic reagin is a true antibody, it is not produced by the organ that gives rise to anaphylactic antibody in human beings. These facts alone should justify the separation of the two forms of hypersensitiveness.

The question as to the nonantigenic nature of some atopens may be tabled until the nature of "drug idiosyncrasy" is determined. However, in whatever way the latter question is decided, it seems hardly possible that this form of human hypersensitiveness will ever be shown to be anaphylactic.

The theory of Wolf-Eisner, who first suggested that drug idiosyncrasy is an acquired hypersensitiveness to a chemical combination of the nonantigenic "drug" with the individual's own body protein, still remains a theory, which has only less foundation than had the theory of the anaphylactic nature of hay-fever and asthma. In other words, it has not even been shown possible, after sensitization of a guinea-pig with the chemical in combination with protein, to shock the animal with the uncombined chemical. Further speculation along the line of the theory of Wolff-Eisner may well afford to await such a demonstration.

The demonstration of the qualitative difference between the anaphylactic antibody and the atopic reagin has placed the argument of the familial character of atopy in a new light, one which makes it appear immaterial whether the atopic character is limited to the 7 or 8 per cent of the population estimated by Cooke and Vander Veer and Spain, or whether, as Ancona and Doerr think, it is present in greater or less degree in all human beings. After all, it is the "reaginogenic organ" that is inherited, and that is responsible for the atopic hypersensitiveness.

Argument number four has lost some ground.

Argument number five, in principle, should be abandoned, though to speak of "desensitization" in human hypersensitiveness would still remain misleading.

The proponents of the anaphylactic nature of atopy seem to have placed too great importance on inconsequential or superficial similarities between these two forms of hypersensitiveness.

Doerr betrays a weakness of his standpoint by identifying an occasional lacrimation in the guinea-pig as hay-fever, and by inviting one to look on the occasional scratching of the nose and other parts of the body by the guinea-pig in some anaphylactic reactions as representing the urticaria of human beings.

A number of investigators have attempted to lend a greater plausibility to the view that the symptoms of bronchoconstriction in the guinea-pig represent asthma by administering the antigen in the form of dust or spray to the sensitized animals by inhalation. The purpose of this form of administration was naturally to show that, like the human subject, the sensitive guinea-pig can be shocked by a direct application of the excitant to the bronchi presumably without having gained access to the blood.

However, the fallacy of this point of view has been exposed in a noteworthy investigation by Alexander,[52] who has found that in every experiment of this kind carried out by him, whenever the induction of shock in the sensitized animal was successful the uterine muscle could be shown to be desensitized. This shows that even by the inhalation method of administration the antigen reaches the bronchial muscles via the blood stream.

This modification of the anaphylaxis experiment represents, thus, only an attempt to set up another superficial resemblance between anaphylaxis and atopy, in disregard of the really important question as to the site and nature of the physiologic reaction by which the respiration is disturbed or interrupted in asthma, on the one hand, and in the anaphylactic shock of the guinea-pig, on the other. This question still remains open.

Koessler [53] has presented histologic evidence intended to support the idea that the asthmatic "attack" is actually a bronchiospasm. Briefly, this evidence consists in a supposedly specific hypertrophy of the broncial muscles in asthmatics.

Before Koessler's [54] interpretation of his findings can be considered, it would seem important to make a similar study of the bronchi in chronic nonasthmatic bronchitis and tuberculosis. The muscular hypertrophy found by Koessler could be looked on as an effect of the asthma rather than as a cause of it.

Harkavy [55] reports that the sputum of asthmatic persons contains substances capable of causing contractions of the uterus of the guinea-pig. Such substances were not found in normal nontuberculous sputum.

In the clinical forms of human hypersensitiveness in which the original lesion is accessible to direct examination (hay-fever, angioneurotic edema and urticaria) that lesion is found to be an edema.

Hence, it may be considered reasonable to assume that in the two important remaining clinical forms (asthma and gastro-intestinal dis-

52. Alexander, H. L.: J. Immunol., to be published.
53. Koessler, K. K.: Arch. Int. Med. **30**:689 (Dec.) 1922.
54. Koessler, K. K.: To be published.
55. Harkavy, J.: Proc. Soc. Exper. Biol. & Med. **22**:225, 1925.

turbance) the primary lesion may likewise be edema. There seems to be no occasion, in either of these two forms, to seek a different mechanism.

In view of the prominence of edema in the pathology of human hypersensitiveness, the recent numerous studies of Petersen, Levinson and Manwaring in this country, as well as those of Schmidt and Barth (cited by Doerr) on the phenomenon of increased endothelial permeability in anaphylactic shock are of immedite interest.

One can look on the latter experiments as raising the question whether the asphyxia of anaphylactic shock in the guinea-pig is due to edema instead of spasm of the bronchial muscles. However, this idea is confronted by the fact that many of the experiments were carried out on the dog and the rabbit, in which animals there is no respiratory asphyxia in anaphylactic shock.

There remains thus to be considered the possibility that the ultimate cause of the asphyxia in the anaphylactic shock of the guinea-pig is different from that of bronchial asthma. In the former instance it is doubtless the muscular bronchiospasm; in the latter, it may be chiefly edematous swelling of the bronchial mucosa.

This situation can be summarized as follows: There is some presumptive evidence pointing to bronchiospasm as the ultimate cause of the asthmatic "attack." None of this evidence, however, is conclusive. The outstanding pathologic lesion of atopy is edema; this must be considered as a probable cause of the asthmatic asphyxia.

Only further confusion can result from the effort to identify certain obscure reactions in lower animals as idiosyncrasy. This identification to which Doerr offers, at least, no objection, is made on the basis of the sole consideration that some of the reactions occurred on a primary injection.

It would be easy to multiply the superficial similarities between atopy and anaphylaxis, most of which are reflections of the fundamental similarity in the underlying mechanism of the two forms; however, about these similarities, there is or should be no dispute. I merely suggest and contend that, in the light of the recently acquired information, the separation of the two forms under an inclusive heading is still practically and scientifically justified.

Doerr's definition of anaphylaxis as an antibody-antigen reaction makes that term practically (though not exactly) synonymous with our term hypersensitiveness, thus leaving the several other recognized forms in a subordinate position wholly inadequate to their biologic and medical importance.

Notes and News

Death of Guiteras.—Juan Guiteras died suddenly at his home in Matanzas, Cuba, October 28, aged 73. Dr. Guiteras graduated from the University of Pennsylvania school of medicine in 1873; was on the staff of the Philadelphia Hospital from 1873 to 1879; in the U. S. Marine hospital service from 1879 to 1889; professor of medicine, Charleston (S. C.) Medical School, 1884 to 1888; professor of pathology at his alma mater, 1889 to 1899; professor of general pathology and tropical medicine, University of Havana, 1900 to 1921; director of the Las Animas Hospital, and from 1909 to 1921, director of public health in Cuba. He was president of the National Medical Congress of Cuba, 1905; secretary of public health and charities, 1921 to 1922, and a member of the Yellow Fever Commission of the International Health Board of the Rockefeller Foundation since 1916. Dr. Guiteras was closely associated with work on yellow fever in the United States and Cuba for many years, and was among the first to confirm the experiments of Walter Reed and his associates on the U. S. Army Yellow Fever Commission.

Askanazy Honored.—*Revue médicale de la Suisse Romande,* number 8 of volume 25, issued June 25, 1925, is dedicated to Max Askanazy in commemoration of his sixtieth birthday and of his twentieth anniversary as professor of pathologic anatomy in Geneva.

Death of Ransom.—Brayton Howard Ransom, chief of the Zoological Division of the Bureau of Animal Industry, died on Sept. 17, 1925, aged 46. Dr. Ransom was a leading parasitologist and made important contributions to our knowledge of parasitic diseases in man and in domestic animals. He is credited with the carbon tetrachloride treatment for hookworm disease.

Library Association Protests High Cost of German Publications.—The executive committee of the American Medical Library Association is making an investigation of the present high cost of German medical publications. It is hoped to determine whether or not concerted action on the part of medical libraries of America will cause German publishers to curtail their output and to reduce the cost of their publications to American purchasers. It is pointed out that many American libraries and publishers have donated subscriptions to German libraries and physicians, but that German publishers have seemed to appreciate but little this evidence of good will. In order to obtain evidence of the interest in some joint action in the matter, those willing to aid in the movement are asked to communicate with Miss Margaret Brinton, librarian, Mayo Clinic, Rochester, Minn.

S. T. Darling Killed in Motor Accident.—Dr. Samuel Taylor Darling, distinguished pathologist and authority on tropical medicine, for the past ten years on the staff of the International Health Board, was killed in a motor accident in Syria, May 20, 1925. He was traveling in the interests of a survey of malarial conditions with the malaria commission of the health section of the League of Nations. Dr. Darling was born in New Jersey, in 1872. From 1906 to 1915 he was chief of laboratories in the Panama Canal Zone; in 1915 he joined the staff of the International Health Board, and from 1918 to 1920 he served as professor of hygiene in Sao Paulo, Brazil. He made important contributions in the field of trypanosomiasis, malaria and hookworm disease.

Depository for Research Materials.—Several years ago the International Association of Medical Museums established a depository of materials used in research at the museum of the medical school of McGill University in Montreal. About three years ago this was transferred to the Army Medical Museum at Washington, D. C., where it is maintained by the curator. The purpose is to preserve in a suitable place materials used in investigations the results of which have been published. Pathologic and bacteriologic slides, gross specimens, photographs, etc., have been deposited, as well as reprints of corresponding articles. Additional material, such as tables or charts not published in full but necessary for the better understanding of published articles, may be included. The cooperation of investigators in medical and allied sciences is desired in order to make this depository of the greatest value. Address the Curator, Army Medical Museum, 7th & B. Sts. S. W., Washington, D. C., from whom additional details may be learned.

Work of Dr. Spaeth — His Successor.—R. A. Spaeth, professor of physiology in Chulalongkorn University in Bangkok, Siam, died June 26, 1925, aged 28, of septicemia contracted during an expedition in the jungle for the purpose of collecting material for study. Before going to Siam Dr. Spaeth was an associate in physiology in the School of Hygiene and Public Health at Johns Hopkins University, and while there carried out studies on the effect of fatigue on infection, under a grant from the committee on scientific research of the American Medical Association.

Hunter Receives Fellowship.—Dr. Warren C. Hunter, for the past four years instructor in pathology, University of Oregon Medical School, and engaged in research in coronary arterial disease, has been awarded a fellowship in pathology by the National Research Council for one year, beginning April 1, 1926. His studies will be pursued under Professor A. S. Warthin in the department of pathology, University of Michigan.

University and Hospital Appointments in Kansas City.—At the University of Kansas School of Medicine, Ferdinand C. Helwig has been promoted to assistant professor of pathology, and Albert S. Welch and Caryl R. Ferris have been appointed as assistants in pathology. Dr. Helwig is pathologist and Dr. Ferris assistant pathologist at Christian Church Hospital in Kansas City, Mo., and Dr. Welch is pathologist at Kansas City (Mo.) General Hospital.

Nebraska Appointments.—Aura J. Miller has succeeded John Jay Keegan as associate professor of clinical pathology in the University of Nebraska College of Medicine. The vacancy was due to the appointment of Dr. Keegan as dean of the medical school in the place of Irving S. Cutter, who has become dean of Northwestern University Medical School in Chicago.

Death of Henry Rose Carter.—Henry Rose Carter, assistant surgeon-general of the U. S. Public Health Service, died on Sept. 14, 1925, aged 73. Dr. Carter was an outstanding pioneer in the control of yellow fever and of malaria. By discovering the period of extrinsic incubation of yellow fever — the period from the time of arrival of infecting cases in isolated houses to the development of secondary cases in such houses — he contributed most significantly to the solution of the problem of causation of this disease and to the introduction of rational methods of prevention. In 1913 he conducted (Roanoke Rapids, N. C.) with marked success the first campaign for control of malaria in this country.

Faculty Appointments at Colorado.—Ralph B. Mills has accepted the appointment of professor and head of the department of pathology in the University of Colorado Medical School. Dr. Mills graduated in medicine at the Johns Hopkins University and was for four years prior to 1924 professor of pathology in the Peking Union Medical College, Peking, China. During the year 1924-1925, he pursued special work in pathology and bacteriology at the University of Chicago.

Ross Whitman, formerly professor of pathology in the University of Colorado, is now professor of bacteriology in the University School of Arts and Sciences at Boulder.

C. H. Elliot, for some years pathologist to the Denver City and County Hospital, has been appointed assistant professor of pathology at the University of Colorado Medical School.

Ivan C. Hall, professor of bacteriology in the New York State College of Agriculture at Cornell University in Ithaca, is now professor and head of the department of bacteriology and public health in the University of Colorado Medical School in Denver.

Abstracts from Current Literature

Pathologic Physiology

[The abstracts have been prepared by the physicians whose names are signed to them. Unsigned abstracts may be credited to the editorial staff.]

ABSORPTION OF UNDIGESTED FROTEIN FROM ALIMENTARY TRACT AS DETERMINED BY DIRECT ANAPHYLAXIS TEST. J. R. HETTWER and R. A. KIRZ, Am. J. Physiol. **73**:539, 1925.

The experimental evidence obtained by Hettwer and Kirz supports the assumption that an unusual increase of intra-intestinal pressure (as a result of stasis) is the essential factor in the absorption, and sufficiently rapid absorption, of an amount of undigested horse serum adequate to cause symptoms of anaphylacic shock in previously sensitized guinea-pigs, or to sensitize normal guinea-pigs, provided the dose is suitably adjusted.

J. A. M. A.

THE BLOOD GLUCOSE CURVE IN HEAD INJURIES. E. C. DAVIDSON and C. I. ALLEN, Bull. Johns Hopkins Hosp. **37**:217, 1925.

The blood sugar curve following the intravenous injection of 25 gm. of glucose was determined in fifteen normal persons, in twelve cases of concussion of the brain and in eighteen cases of fracture of the skull.

The average fasting blood sugar in concussion of the brain and fractured skull was found to be within normal limits. The average blood sugar at the end of fifteen minutes was much higher in persons with concussion of the brain than normally, and the blood glucose curve fell to the fasting level much more slowly. The fifteen minute blood sugar values in persons with fractured skull showed elevations higher even than those seen in concussion, and the fall of the curve to the fasting level was still more delayed.

Subsequent observations on both types of head injury during late convalescence revealed curves quite like those obtained in the control cases and gave no support to the opinion of the traumatic origin of diabetes mellitus.

The more serious the injury, the more striking was the disturbance in the blood sugar reaction following the administration of glucose. No relationship has been observed between the spinal fluid pressure per se and the blood sugar reaction following the administration of glucose.

THE INFLUENCING OF LYMPHOID TISSUE THROUGH NUTRITION AND ITS IMPORTANCE IN PATHOLOGICAL ANATOMY. K. A. HEIBERG, Centralbl. f. allg. Path. u. path. Anat. **36**:433, 1925.

The development of lymphoid tissue can be influenced by changes in diet, and is susceptible to the effects of inanition. In mice, during interrupted adequate diet and gain in weight, the germinal centers were present in large numbers, while during a fall in weight their development was poor. Other factors besides inanition also have some influence. This is seen in the deleterious effect on lymphoid tissue, especially the spleen, of long-continued irradiation in over-doses. The particular injury to the germinal centers of lymphoid tissue by chronic partial inanition has heretofore been imperfectly understood, although this circumstance is undoubtedly of great interest for certain pictures in pathologic anatomy.

B. R. LOVETT.

SEROLOGIC REACTIONS ASSOCIATED WITH EXPERIMENTAL PLETHORA AND PLETHORIC ANEMIA. L. A. JULIANELLE and C. A. PONS, J. Clin. Investig. **1**:519, 1925.

Various hypotheses to explain the blood destruction following experimental plethora were tested by Julianelle and Pons by a number of methods. No evidence was obtained that the blood destruction is the result of the development of isohemolysins or due to greater activity of hemophages. The explanation of post-plethoric anemia must await further investigation.

BLOOD PLATELETS IN SURGICAL DISEASE. H. HUECK, Deutsch. Ztschr. f. Chir. **192**:322, 1925.

Hueck concludes from counts of the platelets in 100 cases that this method does not play a significant rôle in surgical diagnosis. In the first five days after operation a decrease is usually found; then a rise is noticed beyond the normal by the eighth to the eleventh day, and after this a slow return to normal values.

J. A. M. A.

BLOOD SUGAR STUDIES. I. RAPID ALTERATIONS IN THE BLOOD SUGAR LEVEL OF RABBITS AS RESULT OF INTRAVENOUS INJECTIONS OF KILLED BACTERIA OF VARIOUS TYPES. ISOLDE T. ZECKWER and HELEN GOODELL, J. Exper. Med. **42**:43, 1925.

A rapid rise in the blood sugar level of rabbits was produced by intravenous injections of killed *Bacillus proteus, Bacillus coli,* and *Bacillus paratyphosus B,* which returned to nearly the previous level in a few hours.

A less pronounced rise in blood sugar was produced by killed *Bacillus paratyphosus A* and *Bacillus enteritidis.*

BLOOD SUGAR STUDIES. II. BLOOD SUGAR CHANGES IN FATAL BACTERIAL ANAPHYLAXIS IN THE RABBIT. ISODLE T. ZECKWER and HELEN GOODELL, J. Exper. Med. **42**:57, 1925.

During bacterial anaphylaxis there is a gradual rise in the blood sugar level, which attains an extremely high value at the time of death. The curve of blood sugar is almost the same whether anaphylaxis is induced by organisms which affect the blood sugar in the unsensitized animal or by organisms which have no such effect.

No instances occurred in which there was not a marked hyperglycemia in anaphylaxis.

DRAINAGE OF THE THORACIC DUCT IN EXPERIMENTAL PERITONITIS. BERNHARD STEINBERG, J. Exper. Med. **42**:83, 1925.

When care is taken to produce a peritonitis which in itself is almost uniformly fatal, drainage of the thoracic duct in dogs has no favorable influence on the course or result of the peritonitis.

Under the conditions of the experiments the thoracic duct did not serve in any important way as a drainage tract for bacterial contamination of the peritoneal cavity.

AUTHOR'S SUMMARY.

THE RELATION OF HYPERGLYCEMIA TO THE RELATIVE BLOOD VOLUME, CHLORINE CONCENTRATION AND CHLORINE DISTRIBUTION IN THE BLOOD OF DOGS. LEE FOSHAY, J. Exper. Med. **42**:89, 1925.

In normal dogs experimental hyperglycemia causes a prompt dilution of the circulating blood. This is evidenced by the increase in the relative volume of serum and the reduction of the erythrocyte counts. If the hyperglycemia is large, the viscosity of the blood is visibly diminished. As the hyperglycemia increases, there occurs a reduction of the serum chlorine concentration and an increase in the concentration of corpuscular chlorine.

Reduction of an artificial hyperglycemia restores the relative blood volumes to their normal status. The erythrocyte count rises to the normal and the corpuscular chlorine concentration is diminished. If the reduction is a large one, the viscosity of the blood is visibly increased.

The same types of conductivity-chloride discrepancy that occur in human blood are found in the blood of dogs. In addition, a third type is described. Hyperglycemia does not cause the same changes in the volume of the average erythrocyte of the dog as it does in the case of human erythrocytes.

AUTHOR'S SUMMARY.

MODE OF INHERITANCE OF HEREDITARY ATAXIA. W. RUSSELL BRAIN, Quart J. Med. **72**:351, 1925.

Brain asserts that the mode of inheritance of hereditary ataxia cannot be explained on the assumption that the disease behaves as a single mendelian character, whether dominant or recessive. It can be explained satisfactorily if it be assumed that the disease depends on the presence of two mendelian characters, one of which is a dominant and the other a recessive. The percentage of affected offspring expected on this hypothesis is consistent with that actually found.

J. A. M. A.

HEREDITY IN POLYCYSTIC KIDNEY DISEASE. H. W. B. CAIRNS, Quart. J. Med. **72**:359, 1925.

In one family eight, and probably ten, cases of polycystic kidney disease have occurred in three successive generations, comprising forty-two individuals. The fourth generation does not yet manifest any symptoms of the disease.

J. A. M. A.

SEX GLANDS AND METABOLISM. III. INFLUENCE OF INJECTIONS OF TESTICULAR AND OVARIAN EMULSIONS ON NITROGEN AND GASEOUS METABOLISM OF DOGS AND RABBITS. V. KORENCHEVSKY, Brit. J. Exper. Path. **6**:158, 1925.

The effects of castration on nitrogen metabolism, on the one hand, and of injections of testis or of ovaries (without corpora lutea), on the other, observed in most animals, Korenchevsky says indicate that the sex glands probably contain hormones which increase nitrogen metabolism. The varying effects on the nitrogen metabolism obtained after injections of emulsions of testis or of ovaries may possibly be explained by: (1) the presence in them of specific (e. g., corpora lutea in ovaries) or of nonspecific (e. g., insulin-like substances) principles; (2) the varying degree of functional efficiency and, therefore, the varying reaction of the synergetic and antagonistic female animals by the different stages of development of the corpora lutea or of the remaining ovarian

tissue in their own ovaries. Experiments on thyroidectomized animals show that, in spite of the close interrelationship between sexual and thyroid glands, changes in nitrogen increased stimulation of the thyroid gland.

J. A. M. A.

ATTEMPTS TO PRODUCE EXPERIMENTAL INCREASE IN THE RATE OF OUTPUT OF THYROGLOBULIN BY THE THYROID GLAND. A. J. CARLSON, L. HEKTOEN and K. SCHULHOF, Am. J. Physiol. **71**:548, 1925.

Using the specific precipitin test for thyroglobulin, an attempt was made to study possible variations in the thyroglobulin output from the thyroid by massage of the thyroid glands through the skin of the neck, stimulation of the cervical sympathetic nerves for from thirty to sixty minutes, and intravenous injection of epinephrin and pilocarpine in various amounts. In no case was an increase of thyroglobulin produced in the lymph coming from the thyroid gland by any of these procedures. No evidence was secured for the existence of secretory nerves to the thyroid gland by these methods. Probably the thyroid vein is the most important route of the thyroid hormone output, since much greater blood volume passes through the gland than the volume of lymph coming from the gland.

The question of rate of hormone output by the thyroid gland under varying conditions of health and disease is extremely important especially in connection with the diagnosis and therapy of thyroid disorders. Previous methods have not yielded conclusive results. The basal metabolic rate test is reliable only in case of marked hyperthyroidism or hypothyroidism, and it is well known that other conditions (such as nervous instability) may raise the basal metabolic rate so as to simulate mild degrees of so-called toxic goiter.

A. J. CARLSON.

EFFECT OF ORGANIC BRAIN AND SPINAL CORD CHANGES ON SUBARACHNOID SPACE, CHOROID PLEXUS AND CEREBROSPINAL FLUID. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **14**:468 (Oct.) 1925.

The secretion theory of the cerebrospinal fluid holds that this body fluid is largely elaborated by the choroid plexus.

The excretion or absorption theory, in contrast, holds that the fluid comes from the tissue fluids of the brain.

The secretion theory is mainly based on experimental and anatomic data, which may equally well be explained by the excretion theory.

The latter renders understandable the changes in the subarachnoid spaces and choroid plexus in various lesions of the brain or cord.

As the secretion theory does not explain the relationship between the brain and subarachnoid changes, it must be assumed that the cerebrospinal fluid is produced by the brain tissue, the villi of the choroid, like those of the arachnoid, being organs, not of secretion, but of excretion or absorption of the waste from the spinal fluid.

AUTHOR'S SUMMARY.

EXPERIMENTAL STUDIES OF ICTERUS. A. CONTRIBUTION TO THE PATHOGENESIS OF OBSTRUCTIVE ICTERUS. K. HIYEDA, Beitr. z. path. Anat. u. z. allg. Path. **73**: 541, 1925.

In the livers of rabbits and dogs subjected to ligation of the common duct, Hiyeda describes changes which he considers characteristic for the species and

which he believes to be due to anatomic differences in the intrahepatic biliary duct system in the two species. From three to seven hours after ligation of the common duct in the rabbit the liver shows mulitple, small, yellowish-green spots which have a netlike arrangement. This condition, which the author terms "net necrosis" although admitting that it is not a true necrosis, is due to escape of undiluted bile by rhexis at the point of junction of the intralobular canaliculi with the interlobular ducts. In the dog visible jaundice appears later and is less intense than in the rabbit. "Net necrosis" does not occur in the dog. In the latter, from two to three weeks after duct ligation, the peripheral and intermediate zones of the liver lobules appear clear and less deeply stained than the central zone; for this condition Hiyeda proposes the name "clarification." This change is the result of the escape by diapedesis of dilute bile. In the dog the bile canaliculi are more resistant to rupture following obstruction than in the rabbit, and because of the greater degree of damage to the parenchyma in the latter animal through the action of more concentrated bile, obstructive jaundice becomes associated with a more marked proliferative connective tissue reaction than in the dog. Such species differences must be taken into consideration in comparing the results of animal experimentation and in applying them to the human being.

O. T. Schultz.

Research on Favism. C. Lotti and A. Manai, Sperimentale **79**:791, 1925.

In Italian, favism (from the Italian word "fava" meaning bean) is the name of a disease, prevalent especially in Sardinia, that arises from inhalation of the odors of the flowers of the bean plant or from ingestion of the green fruit. The disease is characterized by an icterohemoglobinuric complex. The authors have found that the common bean as well as the kidney bean contains substances that are toxic for rabbits, causing convulsions and more or less marked hemoglobinuria. If the animal survives, biliary pigments and urobilin are found in the urine. The extracts have a strong agglutinating effect on red corpuscles. The juice of bean flowers causes grave general disturbances in rabbits, with convulsions and death; but hemoglobinuria does not result, although urobilin may be present in the urine. The serum of patients with favism who give positive skin reactions to bean extracts sensitizes rabbits when injected intravenously (passive allergy).

Pathologic Anatomy

Studies on Endothelial Reactions. IX. The Formation of Reticulum in the Lesions of Experimental Tuberculosis in Rabbits. Nathan Chandler Foot, Am. J. Path. **1**:341, 1925.

Cellular derivatives of the endothelium seem to play an important part in forming reticulum, for they are always present in its vicinity, but they do not appear to produce it by intracellular activity. Newly formed reticulum seems to be a product of preexisting reticulum, as it is always continuous with it. Fibrin plays no direct part in the production of reticulin.

Reticulin apparently is converted directly into collagen, but the manner in which this transformation is effected has yet to be explained. Caseation and reticulin formation are incompatible; after a preliminary proliferation in areas of early caseation, the reticulum is destroyed. The presence of tubercles in an organ appears to stimulate the growth and to cause a coarsening of the

normal, preexisting reticulum in their immediate vicinity. This might be interpreted as a forerunner of the production of newly formed reticulin fibrils.

More reticulum is produced in those tubercles occurring in or near portions of an organ already rich in that tissue. Conversely, it is scanty in those occurring at some distance from the stroma of the organ.

The importance of collapse in the process of scar formation in chronic tuberculosis of the lung is emphasized in sections impregnated with silver.

THE STATE OF THE CARDIAC MUSCLE IN HYPERTROPHY AND ATROPHY. HOWARD T. KARSNER, OTTO SAPHIR and T. WINGATE TODD, Am. J. Path. **1**:351, 1925.

The enlargement of the heart in hypertrophy is due principally to a hypertrophy of the muscle fibers. The change is accompanied by a distinct tendency toward uniformity in breadth of the fibers. The average breadth is significantly greater than in the normal heart. It would appear that all fibers tend to approximate the larger size, and it is suggested that when all or nearly all the fibers have attained the maximum, further hypertrophy is impossible. What determines the maximum is not disclosed, but the anatomic basis for a "limit of hypertrophy" can be explained on this basis. Presumably, also, the relative reduction of reserve capacity in the hypertrophic heart may be due to the fact that the individual fibers have reached their maximum growth and probably also their maximum functional strength.

The reduction in size of the heart in atrophy is due to a reduction in size and number of fibers. Since there are no fibers whose breadth is less than the narrowest fibers of the normal heart, the change must be due to an atrophic shrinkage and not to longitudinal splitting. In proportion to the number of fibers the number of nuclei in the atrophic heart is increased. This is clearly shown by mathematical calculations and is in accord with Eden's demonstration of relative increase of purine nitrogen in the atrophic heart. This might be regarded as an attempt at regeneration, but no mitotic figures or clear indications of amitotic division were found. The increased number, however, is well established, and must be due to some form of multiplication, but this study gives no information as to the fiber units (or cells) and does not correlate nuclei and fiber units. To elucidate the increased number of nuclei, further work is necessary to demonstrate clearly and uniformly the intercalated disks.

The approach to uniformity in breadth of the fibers of the hypertrophic and atrophic heart as compared with the normal gives a new conception of variability as affecting the cardiac muscles in its adaptation to abnormal conditions.

THE HISTOLOGICAL ALTERATIONS OF THE PANCREAS IN CHRONIC PASSIVE CONGESTION. WILLIAM C. VON GLAHN and ROBERT CHOBOT, Am. J. Path. **1**:373, 1925.

A comparative histologic study of the pancreas has been made in 100 cases of cardiac decompensation and in an equal number of controls.

The distinctive features of chronic passive congestion of the pancreas are: (1) areas of capillary congestion at the periphery of the primary lobules, (2) atrophy of the parenchymal cells in the congested areas, (3) condensation of the connective tissue framework following or accompanying the atrophy of the cells, (4) disappearance of the prezymogen granules in the atrophied cells. It is also characteristic that there is no congestion of the vessels of

the islands of Langerhans, no demonstrable change in the island cells, and no fibrosis in the congested portions.

The intensity of these changes in the pancreas follows closely that in the liver in chronic passive congestion, and is directly related to the duration of the final period of cardiac decompensation.

There is no evidence to support the belief that chronic interstitial pancreatitis follows chronic passive congestion of the pancreas.

MUCOCELE OF THE APPENDIX WITH GLOBOID BODY FORMATION. GIBBS MILLIKEN and C. A. POINDEXTER, Am. J. Path. **1**:397, 1925.

The etiology of mucocele of the appendix is rather obscure. Elbe has given as conditions for its development the following: First, a slowly stenosing process at one or more points of the lumen. A rapid stenosis produces gangrene. Second, a sterile lumen must be present distal to or between the points of stenosis. Bacterial invasion, if of sufficient virulence, would cause a secondary empyema of the appendix. Third, there must be an actively secreting mucosa, or at least a more rapid secretion than absorption, and also some change in the mucosa whereby the normal mucus is transformed into pseudomucin.

In the globoid form these features are essential, but an additional one is also present, the mucoid material being excreted from the crypts, as suggested by Shattock. An inflammatory reaction is of considerable importance as a stimulus to hypersecretion of mucin, and all of the cases collected that were studied microscopically presented this feature except the one reported by Morrison.

Mucocele of the appendix is infrequent. The globoid body type of mucocele of the appendix makes up only 0.35 per cent of the reported cases. This unusual form probably represents a combination of secretion of mucus into the crypts and some disturbance of reabsorption of the secreted material, plus a chemical change whereby normal mucus is transformed into pseudomucin. In less than half of the reported cases the patients had symptoms referable to the appendix during life, the condition being frequently an accidental finding at necropsy or during an exploratory abdominal operation.

ON THE NATURE OF MITOCHONDRIA. J. E. WALLIN, Am. J. Anat. **35**:403 and **36**:131, 1925.

The conclusion that mitochondria are polymorphic bacterial organisms symbiotically combined with cells, is upheld.

L. HEKTOEN.

SUDDEN DEATH DUE TO EXACERBATION OF LATENT SYPHILITIC MYOCARDITIS. A. S. WARTHIN, Am. Heart J. **1**:1, 1925.

Eight cases are described showing that sudden death may occur in latent syphilis as the result of an acute exacerbation of previously mild, latent processes in the heart and aorta. The active lesions differ from the chronic in more marked edema and the greater polymorphonuclear cell content of the infiltrations. In this respect the acute lesions resemble the infiltrations of active syphilis of the umbilical cord in which the cells are predominantly polymorphonuclears and the number of spirochetes enormous; the lesions correspond also to the "critical reaction" of Wade Brown and Louise Pearce in syphilis in animals in which there is a diffuse edema and polymorphonuclear infiltration in the rapidly developing lesions followed by a rapid resolution. Acute

and active syphilis is characterized by diffuse lesions, marked edema and a great number of polymorphonuclear cells in the infiltration; the typical picture of perivascular lymphocyte and plasma cell infiltration and eventually fibrosis will, however, always be associated with these when the active process is an exacerbation of an older latent syphilis. According to Brown, the polymorphonuclear infiltration of the critical reaction is just as typical for syphilis as is the focal round cell infiltration for the chronic type of syphilitic process. This fact may not be recognized by the pathologist who carries in his mind the mononuclear type of infiltration as the characteristic diagnostic picture of syphilis; and he may, therefore, fail to recognize the polymorphonuclear malignant type of syphilis. At any rate, the demonstration of the spirochete in the latter type of lesion is the only decisive diagnostic point, and must be accomplished to fix the diagnosis; unless this is done, such cases will escape proper interpretation. Unfortunately for the recognition of these cases, routine examinations for spirochetes are made in few pathologic laboratories.

The factors leading to increase of virulency in chronic latent cases are still unknown, beyond the vague conception of lower resistance due to overstrain, fatigue, other infections and intoxications, etc.

Much is being said at present about the frequency and apparent increase of cardiac disease, but the important, if not predominant, rôle played by syphilis in the production of myocardial incompetency is not recognized by the major part of the profession, internists as well as pathologists. While some physicians of large experience are fully aware of the importance of syphilitic myocardial changes, others fail to recognize it; and the same is true of pathologists.

In Warthin's experience in Michigan, syphilitic cardiovascular lesions are common, and are more frequently associated with cardiac incompetency than is coronary disease or streptococcus, rheumatic, diphtheric or typhoid myocarditis. The systemic examinations of hearts of patients with paresis, tabes and syphilis of long standing will show characteristic myocardial lesions in practically every one. Old latent syphilis is one of the most, if not the most, important causes leading to myocardial incompetency; and the person with latent syphilis in the great majority of cases eventually dies a "cardiac failure" death. Acute exacerbations of a previously latent syphilis or an acute malignant type of cardiac syphilis are much less common than in the chronic latent forms, but the frequency remains to be determined, as such exacerbations have not received pathologic recognition.

L. HEKTOEN.

THROMBOSIS AND EMBOLISM. J. A. VIETOR, Ann. Surg. **82**:193, 1925.

Vietor has studied twenty-one cases of fatal pulmonary embolism occurring in 12,615 operations. Necropsies were obtained in nine cases and showed a thrombosis of the femoral vein in four cases. In one case there was a thrombosis of the common iliac vein and the inferior vena cava. In two cases a wound inspection only was allowed, so the condition of the femoral veins was undetermined. In the remaining two cases, while a complete necropsy was performed, no existing thrombosis could be demonstrated. The patients who died of a pulmonary embolus gave no clinical sign of a preexisting phlebitis or thrombosis, except in a case of carcinoma of the pancreas. In this case the patient had a hopeless condition and was gradually dying of a metastatic growth in the liver. On the thirteenth postoperative day a swelling of the left leg was first noted, and on the twenty-seventh day hemiplegia developed. Death occurred on the thirty-first day after operation apparently from cachexia,

but at necropsy a large pulmonary embolus with thrombosis of the common iliac and inferior vena cava was revealed. One patient with inguinal hernia complained of a pain in the right leg on his third postoperative day, but periodic examination was negative for clinical evidence of a phlebitis. He died on the eleventh day, and at necropsy a thrombosis of the right femoral vein was found.

J. A. M. A.

Some Cystic Formations of the Spinal Dura Mater and Their Pathogenetic Interpretation. P. Verga, Sperimentale **79**:763, 1925.

Cystic formations in the epidural space connected with the external surface of the dura and situated a little below the exit of the spinal roots are described. They are interpreted as the result of arachnoid proliferations in the vicinity of a vessel in the dura, so that a space is formed through which arachnoid fluid can penetrate.

Ocular Lesions in Nephritis. L. Melanowski, Trav. d. Inst. d'anat. path. d. Univ. de Pologne **1**:278, 1925.

Ocular lesions were found in 15 per cent. of cases of nephritis studied. Two types occur: one in cases of nitrogen retention, the other in cases of chlorid retention.

In nitrogen retention there is little edema, the optic disk is congested, the arteries thin, the veins engorged. There is a slight amount of exudate, but ecchymoses are frequent. White patches may be seen in the walls of the retinal vessels. The rods and cones are little changed. The arteries of the iris, choroid and retina are narrow and show hyaline degeneration of the walls. Edema is slight, degenerative lesions and ecchymoses marked. The patient can see and discern colors relatively well.

In the chlorid retention type, edema holds the chief place. The iris is swollen, the pupil is small, posterior synechiae may be seen. All layers of the retina are edematous, and a large amount of exudate is present. Vision and discernment of colors is much impaired.

The two forms may occur together, the fundus showing edema with vascular changes and ecchymoses.

The causes of ocular lesions in nephritis are: general intoxication, hydrocephalus, (consequence of the action on the choroid plexus of retained poisons), vascular changes with hypertension, and anemia. The finding of ocular lesions means a grave prognosis.

The existence of the two types indicates that vascular lesions are not alone responsible; intoxication also has its influence. The ocular lesions, like those elsewhere in the body, are not inflammatory, but congestive and degenerative.

B. R. Lovett.

Sclerosis of Pulmonary Artery. F. C. Arrillaga, Rev. méd. Latino-Americana **10**:1097, 1925.

Arrillaga gives thirteen plates showing the clinical and microscopic aspect of Ayerza's disease. He regards it as a primary affection of syphilitic origin, while Ayerza assumes that it is secondary to some chronic pulmonary lesion. The hypertrophy of the right ventricle and the histologic lesions and enlargement of the pulmonary artery entail the extreme cyanosis of these "black cardiacs," the dyspnea, polycythemia, hemoptysis and angina pectoris. Oblique roentgen-ray examination is most instructive.

J. A. M. A.

SPONTANEOUS RUPTURE OF GASTRO-EPIPLOIC ARTERY. M. BUDDE, München. med. Wchnschr. **72**:1383, 1925.

A man, 23 years of age, suddenly became ill with violent pains in the abdomen. He had never been sick before, and had a negative Wassermann reaction. A perforated ulcer or acute fat necrosis of the pancreas was suspected. He was operated on the following day. Budde found that he had a rupture of a branch of the left gastro-epiploic artery. The artery was ligated, and the patient recovered fully. There had been no trauma before the attack of pain.

J. A. M. A.

ANATOMIC FINDINGS IN MONGOLIAN IDIOCY. A. GANS, Nederlandsch Tijdschr. v. Geneesk. **2**:922, 1925.

Gans says that he has found up to eighty different kinds of malformation in cadavers of mongoloid idiots. The brains show the brachycephalic formation of the Chinese brains examined by Kappers, only in a more pronounced form — "more Mongolian than the Chinese." The weight of the cerebellum was always subnormal, and a mass of nerve tissue — gray matter — was found on the median side of the flocculus. This *tuber flocculi* has been described by others as heterotopia in the cerebellum. It has been noted in congenital myoclonia, and something of the kind was evident in a chimpanzee and an orang-outang Gans examined.

J. A. M. A.

VARIETIES AND THE SIGNIFICANCE OF GIANT CELLS. H. E. JORDAN, Anat. Rec. **31**:51, 1925.

The main results of this effort to coordinate the observations on various types of giant cells in mammalian and higher vertebrate tissues are summarized by the author as follows:

Giant cells
- *A.* Hemogenic ("megalokaryocyte")
  - Origin: hemoblasts, endothelium
  - Location: yolk sac, liver, red bone marrow, spleen, thymus, lymph nodes
  - Function: blood platelet ancestor; multiple erythroblasts
  - 1. Mononucleated (megakaryocytes)
  - 2. Polymorphonucleated (polymorphokaryocytes)
  - 3. Polynucleated (polykaryocytes)
- *B.* Phagocytic
  - Origin: mesenchyme, reticular cells, osteoblasts, osteocytes, lymphocytes, hemoblasts, endothelial cells
  - 1. Osteolytic — osteoclasts
  - 2. Chondrolytic — chondroclasts
  - 3. Odontolytic — ondontoclasts
  - 4. Foreign body
- *C.* Degeneration syncytia

The sources for the data are given in a bibliography. The study shows the high degree of functional adaptability of mesenchymal derivatives and the enhancement of phagocytic capacity following cell fusions.

CONGENITAL DUODENAL SEPTUM WITH OBSTRUCTION. S. M. SEIDLIN, Bull. Johns Hopkins Hosp. **37**:328, 1925.

The occlusion in this case was caused by a perforate iris-like septum stretched across the lumen of the duodenum at the site of the ampulla of Vater. The patient, a child, had lived an apparently normal life for two and one-half

years in spite of the septum. While breast fed and given soft diet, the food easily passed through the small opening in the septum, but the use of coarser food had produced an acute obstruction of this opening. The etiology of this and similar occlusions is discussed.

O. T. SCHULTZ.

CONGENITAL CYSTS OF THE LUNG. AMOS R. KOONTZ, Bull. Johns Hopkins Hosp. **37**:340, 1925.

This appears to be the first recorded American case of congenital cysts of the lung. From the European literature, mostly German, the author has collected 108 cases, which are tabulated. In the case reported constriction of the bronchioles with dilatations of the distal parts had lead to multiple cyst formation. The constrictions of the bronchioles depended on the excessive development of the mucous membrane, the possible causes of which are discussed on the basis of the tentative explanations advanced in previous reports.

O. T. SCHULTZ.

HODGKIN'S DISEASE AND AMYLOIDOSIS. H. SCHALONG, Virchows Arch. f. path. Anat. **257**:15, 1925.

Schalong reports a case of lymphogranulomatosis of the supraclavicular lymph nodes and spleen, with generalized amyloidosis. Since syphilis, tuberculosis and chronic bone disease could be excluded, the amyloid change was believed to be the direct result of Hodgkin's disease. The literature contains twenty-seven previously reported cases of lymphogranulomatosis associated with amyloidosis.

O. T. SCHULTZ.

ENDOMETRIOSIS OF THE FEMALE GENITALIA. R. DE JOSSELIN DE JONG and K. DE SNOO, Virchows Arch. f. path. Anat. **257**:23, 1925.

De Jong presents a detailed microscopic study of a series of examples of so-called adenomyoma of the uterus and ovary. Most interesting in the series are three uteri removed at or near the end of pregnancy and six ovaries removed during pregnancy; in these the misplaced endometrial tissue had undergone a decidual reaction similar to that which occurs in the normal endometrium during ectopic pregnancy. The term endometriosis is accepted for the diffuse form and endometriomyoma for the nodular form. Sampson's conception of the origin of endometriosis of the ovary and pelvic organs as the result of misplacement of endometrial tissue during menstruation is not accepted. The tissue, when present in the uterus, either in diffuse or nodular form, is held to be derived from the differentiated endometrium, and when present elsewhere, from coelomic derivatives which retain the potentiality of forming müllerian duct tissues. De Snoo discusses at length the clinical manifestations of the condition.

O. T. SCHULTZ.

PSEUDOMEMBRANOUS PHARYNGITIS. W. ANTHON, Virchows Arch. f. path. Anat. **257**:96, 1925.

Anthon discusses the differential characteristics of tuberculous, syphilitic and herpetic pseudomembranous pharyngitis. The last named form, which he considers a rare but characteristic one, he believes to be due to secondary infection of herpetic vesicles of the buccopharyngeal mucosa.

O. T. SCHULTZ.

NEUROGENIC ORIGIN OF PEPTIC GASTRIC ULCER. B. N. MOGILNITZKY, Virchows Arch. f. path. Anat. **257**:109, 1925.

In a study of four necropsy cases of gastric ulcer, Mogilnitzky paid especial attention to the vegetative nervous system, in which were found regressive and atrophic changes in the ganglion cells and proliferation of glia. Although the evidence for a neurogenic origin of peptic ulcer is held to be inconclusive, accumulating data indicate the possibility of participation of the nervous system.

O. T. SCHULTZ.

CONGENITAL CYSTIC KIDNEY AND DEFECT OF DIAPHRAGM. H. HOOK and H. U. KALLIUS, Virchows Arch. f. path. Anat. **257**:202, 1925.

The association of a congenital cystic left kidney with congenital absence of the left half of the diaphragm lead to the conclusion that the cystic kidney resulted from a factor acting locally on the posterior abdominal wall in the region of the primitive kidney. Cystic kidney arises from renal tubules which remain rudimentary as the result of an embryonic maldevelopment which inhibits normal differentiation of the tubules.

O. T. SCHULTZ.

ENTEROGENOUS ORIGIN OF ACUTE YELLOW ATROPHY OF LIVER. P. HEILMANN, Virchows Arch. f. path. Anat. **257**:229, 1925.

This is a theoretical discussion of the question whether it is possible to determine whether the noxious agent which causes liver damage varying in intensity from acute yellow atrophy to atrophic cirrhosis reaches the liver through the general or the portal circulation, both possibilities being admitted. In certain cases in which there is no evidence of gastro-intestinal changes, the enterogenous origin of the liver damage may be established by alterations in the mesentery.

O. T. SCHULTZ.

ISLET ADENOMA, CYSTADENOMA AND METASTATIC SARCOMA OF THE PANCREAS. F. J. LANG, Virchows Arch. f. path. Anat. **257**:235, 1925.

Lang reports one case each of nodular adenomatous hyperplasia of the islets of the pancreas, cystadenoma of the pancreas and metastatic spindle cell sarcoma of the pancreas. In the last case as in the first, there was marked increase in the islet tissue. Lang concludes that the islet tissue may multiply, that it arises from duct epithelium and that it is independent of the acinar tissue of the pancreas.

O. T. SCHULTZ.

CHANGES IN UTERINE ARTERIES FOLLOWING PREGNANCY. F. WERMBTER, Virchows Arch. f. path. Anat. **257**:249, 1925.

Wermbter studied the changes which occur in the vessels of the pregnant uterus at various periods of pregnancy and in women whose pregnancy varied at the time of examination from the first to the eleventh. The primary change noted was swelling and degeneration of the media. This is followed by compensatory diffuse or nodular thickening of the intima. The newly formed chromotropic intimal tissue is believed to have close relationship to elastic tissue, fine fibrils of which in time make their appearance and ultimately unite

to form elastic lamellae. After the fifth pregnancy elastic tissue is also laid down in the perivascular connective tissue. The author does not accept Goodall's view of the reformation of the arteries after each pregnancy, but concludes that there is a gradual transformation of the arteries which becomes more marked with each pregnancy. In this transformation the chromotropic intercellular substance of the intima and of the adventitia plays the chief rôle.

O. T. Schultz.

Basal Cell Hyperplasia of the Prostate. E. Krompecher, Virchows Arch. f. path. Anat. **257**:284, 1925.

Krompecher applies to the prostate his frequently reiterated conception of the independent proliferation of the basal cell layer of epithelium. He claims that in 45 per cent of the prostatic hypertrophies of adults it is the basal cell layer which proliferates, primarily as a regenerative process following inflammatory changes. He proposes a classification of prostatic carcinoma into adenomatous and solid; the former he subdivides into basocellular, rotundocellular or adenocellular and cylindrocellular, and the solid forms into basocellular, rotundocellular or adenocellular, and spinocellular, or keratinizing.

O. T. Schultz.

Histologic Study of Testes of Sexual Delinquents. B. Slotopolsky and H. R. Schinz, Virchows Arch. f. path. Anat. **257**:294, 1925.

A careful histologic examination was made of the testes of eight men who had been subjected to castration because of sexual irregularities, with the view of determining changes, especially in the interstitial cells of Leydig, which might explain the abnormal sex activities. In the normal testis the semniferous tubules, the interstitial connective tissue and the interstitial cells make up respectively, 70, 20 and 10 per cent of the volume of the organ, but in areas of variable size, even in the normal testis, variations occur which must be considered as falling within the range of normal. The testes of the sexual delinquents examined by them showed no greater variation than occurs in the normal organ. They therefore disagree sharply with Steinach, who ascribed sexual irregularities in the male to the stimulus of an increased amount of interstitial tissue. The sexual delinquent suffers, not from a biologic constitutional abnormality which has an anatomic basis in the testis, but from psychologic abnormality characterized by lowered cerebral inhibition. The improvement in the conduct of such a person which follows castration is purely symptomatic and is not due to the removal of abnormally active gonads.

O. T. Schultz.

Organ Weights of Normal Rabbits. Wade H. Brown, Louise Pearce and Chester M. Van Allen, J. Exper. Med. **42**:69, 1925.

In November, 1921, a systematic study of normal rabbits was undertaken as a part of a more general investigation dealing with the subject of the animal organism in relation to disease. The present paper on organ weights is based on results obtained from a study of 350 male rabbits killed and examined between Jan. 1, 1922, and July 1, 1924. Methods of conducting the experiments are described and the results are summarized in the form of a table and a series of text figures. The organs studied were the heart, liver,

kidneys, spleen, thymus, testicles, brain, thyroid, parathyroids, suprarenals, hypophysis, pineal gland, and representative groups of lymph nodes.

The results recorded include maximum, minimum and average weights, the median, the mode, the standard deviation, the probable error, the coefficient of variation and the percentage distribution of organs of different weights. No final conclusions are drawn, but it is pointed out that the results obtained are comparable to those that have been reported from similar studies of organ weight in man. Attention is also directed to the tendency to the occurrence of wide variations in the weights of nearly all organs, and to an apparent difference in the degree of correlation that exists between organ weight and body weight in the case of certain organs. In this connection it is pointed out that within certain limits the weight of the brain, in particular, and of other organs to a lesser degree, appears to be independent of body weight.

The results recorded in this paper are regarded as representing approximate values which are affected by numerous conditions for which correction should be made. These conditions will be considered in subsequent papers.

AUTHORS' SUMMARY.

ARCHITECTURE OF GRAY MATTER OF SPINAL CORD. I. RASDOLSKY, Virchows Arch. f. path. Anat. **257**:356, 1925.

The author describes a new technical method for the study of the finer architecture of the intercellular substance of the gray matter of the spinal cord. The application of the method leads him to conclude that the union between neurons occurs by contact rather than by continuity of fibrils.

O. T. SCHULTZ.

SPINA BIFIDA. H. MATHIS, Virchows Arch. f. path. Anat. **257**:364, 1925.

Mathis gives a detailed study of nine examples of spina bifida, paying particular attention to the abnormality of the vertebral column as a whole in an attempt to explain the genesis of the deformity. He believes, in agreement with Ernst, that the causative factor, whether mechanical, thermic or chemical, acts primarily on the medullary groove, the bony changes being secondary.

O. T. SCHULTZ.

EFFECTS OF OBSCURE LESIONS ON ORGAN WEIGHTS OF APPARENTLY NORMAL RABBITS. WADE H. BROWN, LOUISE PEARCE and CHESTER M. VAN ALLEN, J. Exper. Med. **42**:163, 1925.

A group of 350 normal rabbits was studied with reference to the occurrence of obscure lesions of various kinds and the probable or possible effect of such lesions or disease processes on organ weights. The results of the investigation are presented in the form of comparative tabulations.

It was found that so long as the animals remained in apparently good health the values obtained for organ weights of animals with lesions did not differ materially from those for animals that were entirely free from lesions. There were, however, slight deviations from the normal, which appeared to be significant in that they suggested a functional response similar in character to the more marked changes in mass and mass relationships that occur in rabbits presenting clinical symptoms of disease due to the same causes.

AUTHORS' SUMMARY.

THE ORIGIN OF THE CELLS IN THE EXUDATE IN CASEOUS PNEUMONIA. W. PAGEL, Beitr. z. klin. Tuberk. **61**:221, 1925.

The particular necrobiotic phase in which these cells are usually seen suggests the supposition that they are of homogenous origin; but exact study of young forms, considering all fine cellular structure, is rather indicative for the same heterologous origin as for the epithelioid cells which they closely resemble. It was not possible in these studies to find structures which would definitely establish a connection between these cells and myeloic or alveolar cells. In the guinea-pig lung, however, the majority of, or all, exudate cells take their origin from alveolar epithelial cells.

MAX PINNER.

TUBERCULOUS OSTEOMYELITIS OF THE TIBIA. H. KÜMMELL, JR., Beitr. z. klin. Tuberk. **61**:372, 1925.

A woman, aged 80, had a tumor of the size of two fists on her left leg. It contained a hemorrhagic purulent exudate. The necropsy showed a tuberculous osteomyelitis in the diaphysis of the tibia.

MAX PINNER.

THE QUESTION OF CHANGES IN THE HYPOPHYSIS IN DIABETES MELLITUS. ERIK J. KRAUS, Centralbl. f. allg. Path. u. path. Anat. **36**:305, 1925.

The author finds changes in the hypophysis of many diabetic persons and considers the changes specific for that disease. The organ is decreased in size (weight in normal persons about 0.62 gm., in diabetics 0.54 to 0.58 gm.); the eosinophils are fewer in number and smaller in size, and the cells show degeneration. The changes are inconstant and irregular, but they cannot be overlooked.

B. R. LOVETT.

A CLASSIC CASE OF TOTAL PERSISTENCE OF THE TRUNCUS ARTERIOSUS. W. KLEMKE, Centralbl. f. allg. Path. u. path. Anat. **36**:307, 1925.

Only seven instances of this anomaly have been described. In this case, a single large artery arose from the two ventricles, having three valve leaflets at its beginning. It gave off first the pulmonary arteries, then the usual branches of the aorta. There was a large opening in the interventricular septum. During life, the patient was always slightly blue and short of breath. He died at the age of 26.

B. R. LOVETT.

ARTERY OF KEITH AND FLACK'S NODE. E. GÉRAUDEL, Presse méd. **33**:1283, 1925.

Géraudel gives an illustrated description, emphasizing the connection between functional changes in Keith and Flack's node and a disturbed blood supply. He believes that the artery is a terminal artery, analogous to arteries in the brain.

Pathologic Chemistry

THE CHEMICAL COMPOSITION OF THE SPINAL FLUID. HERBERT B. WILCOX, JOHN D. LYTTLE and J. E. HEARN, Am. J. Dis. Child. **30**:513, 1925.

Normal chlorid content of arachnoid fluid runs from 690 to 720 mg. per one hundred cubic centimeters. Low values occur in acute and tuberculous meningitis. The normal protein content is from 30 to 80 mg. per one hundred

cubic centimeters; it is increased in acute and chronic inflammations of the meninges and brain and in altered metabolic conditions in infections and nephritis. The sugar in arachnoid fluid is relatively from 40 to 60 per cent of the blood sugar. Higher values are present in epidemic encephalitis, convulsions, acidosis, nephritis, epidemic poliomyelitis and also in certain normal cases. Low values obtain regularly in acute and tuberculous meningitis. The calcium and phosphorus in the arachnoid fluid bear no relation to their content in the blood or to the clinical state.

THE CONTENT OF TOTAL FATTY ACID AND CHOLESTEROL IN THE SERUM OF SYPHILITIC RABBITS. SHIRO ITO, Acta dermat. **6**:395, 1925.

The author determined the lipoid content in the blod of male rabbits before inoculation with spirochetes, and at ten day intervals afterward. In most of the animals, the total fatty acids decreased at first at the end of three to four weeks, then increased and remained at the high level. The cholesterol decreased and remained low.

B. R. LOVETT.

NITRITURIA. ROY M. GREENTHAL, Am. J. Dis. Child. **30**:321, 1925.

A positive nitrite reaction in freshly passed urine is present at times in about 50 per cent. of cases of pyuria due to nitrate-reducing organisms. A positive reaction is valuable as an aid to diagnosis, but a negative reaction has no significance. The failure of the nitrate test in these cases is due chiefly to a lack of nitrate salts in the urine.

In order to obviate the necessity of carrying about two solutions for the Griess-Ilosvay test, an attempt was made to prepare the reagent in a powder form. The following powder was prepared: sulphanilic acid, 0.5 gm.; anaphthylamin, 0.2 gm.; citric acid, 5 gm.; and lactose, 10 gm. This powder was placed in capsules (No. 0) and the test was performed by emptying the contents of one capsule in 5 cc. of urine. The reagent in powder form was found to be as satisfactory as the liquid and much more convenient to use in bedside tests.

J. P. PARSONS.

DIAZO AND UROCHROMOGEN REACTIONS IN BLOOD FILTRATE. E. BECHER, Deutsch. Arch. f. klin. Med. **148**:10, 1925.

CHROMOGENS IN GRANULAR ATROPHY OF KIDNEYS. E. BECHER, Ibid. **148**:46, 1925.

UREMIA AND RENAL INSUFFIENCY. E. BECHER and F. KOCH, Ibid. **148**:78, 1925.

The filtrate obtained after deproteinizing the blood with trichloracetic acid gives a distinct diazo and a urochromogen reaction in cases of severe renal insufficiency. Becher believes that these reactions are caused by aromatic oxyacids and by oxyproteinic acids.

In patients with severe renal insufficiency, urochromogen and other chromogens are found in the serum and in the urine. The appearance of these substances in the blood parallels the retention of indican, phenol, etc. Becher believes that the light color of the urine from these patients is due partly to the retention of chromogens in the blood and in the tissues, and partly to an inability of the kidney to oxidize these propigments to pigments.

In renal insufficiency a parallelism exists between the retention of phenol bodies (phenol, cresol, diphenols and aromatic oxyacids) and the appearance of true uremic symptoms. Uremia is much less dependent on the retention of protein cleavage products. Since phenol poisoning resembles true uremia, Becher and Koch believe that the phenol derivatives play an important rôle in the pathogenesis of uremia.

J. A. M. A.

Microbiology and Parasitology

STUDIES ON TUBERCULOUS INFECTION. X. THE EARLY DISSEMINATION OF TUBERCLE BACILLI AFTER INTRACUTANEOUS INOCULATION OF GUINEA-PIGS OF FIRST INFECTION. H. S. WILLIS, Am. Rev. Tuberc. **11**:427, 1925.

Guinea-pigs were infected intracutaneously with tubercle bacilli, and the skin with the site of infection was excised (15 to 18 mm. in diameter) at various intervals. Then the appearance and development of changes in the lymph nodes in the axilla and groin were closely watched. It was found that the tubercle bacilli disseminated rapidly from the point of the intradermal inoculation; after three hours some of the bacilii had always migrated beyond the excised area, and they reached the axillary and inguinal lymph glands — about 5 cm. distance from the inoculation — within twenty-four hours.

MAX PINNER.

STUDIES ON TUBERCULOUS INFECTION. XI. THE EARLY DISSEMINATION OF TUBERCLE BACILLI AFTER INTRACUTANEOUS INOCULATION OF IMMUNE GUINEA-PIGS OF REINFECTION. H. S. WILLIS, Am. Rev. Tuberc. **11**:439, 1925.

In this series of experiments immune guinea-pigs prepared by an infection with strain R1 were subjected to the same procedures as the normal animals in the preceding paper. It was found that in the immune animals the dissemination of bacilli is much less rapid and that they usually do not develop tuberculosis after an early excision of the infected skin area. The transportation of bacilli from the site of infection to the regional lymph node requires a little less than three weeks. This confirms Krause's theory "that specific immunity to tuberculosis is accomplished in part throuugh a fixation of bacilli of reinfection by the rapid inflammatory response of the allergic reaction."

MAX PINNER.

THE QUESTION OF CONGENITAL INFECTION WITH SPIROCHAETA RECURRENTIS IN MICE. M. Abe, Acta dermat. **6**:351, 1925.

The author injected into pregnant female mice the spirochetes of relapsing fever, and examined the blood and organs of fetuses taken from the uterus and of the new-born animals for the presence of spirochetes. None was found. New-born mice were found to have no special resistence to spirochetal infection. The conclusion is that spirochetes do not pass the placenta.

B. R. LOVETT.

PUNCTURE OF LYMPH GLANDS IN SYPHILIS. T. Shimoda, Acta dermat. **6**:413, 1925.

A 1 to 2 cm. syringe with a sharp needle containing from 0.1 to 0.3 c.c. of physiologic sodium chlorid is used to puncture the gland. After twisting the

needle about a little, the solution is injected and withdrawn several times. A drop of the fluid is used for examination with the dark field. Of thirty syphilitic patients examined in the primary stage, positive results were obtained in twenty-one.

B. R. LOVETT.

DEMONSTRATION OF ANTIGENIC RELATIONSHIPS AMONG STRAINS OF STREPTOCOCCUS ERYSIPELATIS BY INTRADERMAL PROTECTION TESTS. K. E. BIRKHAUG, Bull. Johns Hopkins Hosp. **37**:85, 1925.

Intradermal infiltration of the skin of rabbits with immune erysipelas serum twenty-four hours previous to the injection of hemolytic streptococci of erysipelas and nonerysipelas origin, Birkhaug says, offered adequate protection against 93 per cent of cultures of erysipelatous streptococci. Immune erysipelas serum offered no local passive immunity against the injurious action of cultures of nonerysipelas hemolytic streptococci. Intradermal infiltration with immune scarlatinal serum twenty-four hours previous to the injection of hemolytic streptococci isolated from throat secretions of scarlet fever patients offered local protection against the injurious action of the homologous and heterologous cultures of scarlatinal streptococci. Immune scarlatinal serum offered no local passive immunity against the injurious action of cultures of nonscarlatinal hemolytic streptococci. Intradermal infiltration with normal rabbit serum did not protect against the injurious action of intradermally injected hemolytic streptococci in the doses used. Antigenic relationships demonstrable by agglutination and agglutinin absorption tests were confirmed with regularity by in vivo local passive immunity experiments. Birkhaug says that by this method of local passive immunity it is possible to differentiate a group of hemolytic streptococci causing erysipelas from a group of hemolytic streptococci responsible for scarlet fever, on the one hand, and on the other, from the large series of miscellaneous hemolytic streptococci producing a variety of pyogenic infections.

J. A. M. A.

SPOROTHRIX INFECTION OF LARGE INTESTINE AND FINGER-NAILS. T. R. BOGGS and H. FRIED, Bull. Johns Hopkins Hosp. **37**:164, 1925.

Boggs and Fried relate the occurrence of an acute and severe dysentery associated with the presence of a sporothrix-like organism in the stools in great numbers, and the clearing up of the condition coincidently with the destruction of the organisms by an antiseptic dye, thus seemingly justifying the tentative association of these as cause and effect. This is further strengthened by the fact that the organism belongs evidently to a group which has furnished pathogenic strains affecting the lungs, skin and lymph glands in numerous reported cases from widely scattered regions of the world. Additional interest is given this case from the association of a mycotic infection of the finger-nails for years preceding the acute intestinal infection with the same organism. It is conceivable, at least, that the patient had taken spores into her intestinal tract for years as a result of biting her nails, and that some incidental factor may have determined the implantation of the organism on the intestinal mucosa. This factor may have been a change in the intestinal resistance, through traumatic or toxic agencies, or an alteration in the virulence in the organism itself.

J. A. M. A.

MICROBIC VIRULENCE AND HOST SUSCEPTIBILITY IN PARATYPHOID-ENTERITIDIS INFECTION OF WHITE MICE. VIII. THE EFFECT OF SELECTIVE BREEDING ON HOST RESISTANCE. FURTHER STUDIES. LESLIE T. WEBSTER, J. Exper. Med. **42**:1, 1925.

Survivors of an experimental mouse typhoid infection, selected and bred for a number of consecutive generations, give birth to offspring which are more resistant to the disease than a random group of the same inbred race.

Offspring of females most susceptible to this infection give birth to individuals which are more susceptible than a group of similar unselected mice.

AUTHOR'S SUMMARY.

STUDIES IN EXPERIMENTAL SYPHILIS. III. FURTHER OBSERVATIONS ON THE POSSIBILITY OF CURE OF SYPHILIS IN THE RABBIT WITH ARSPHENAMINE. ALAN M. CHESNEY and JAROLD E. KEMP, J. Exper. Med. **42**:17, 1925.

Syphilitic rabbits can be treated with arsphenamin in such a manner as to render the lymph nodes incapable of transmitting the infection to normal rabbits. This can be accomplished if treatment is begun either early or comparatively late in the course of the disease. If treatment is begun early, the animals are almost uniformly susceptible to a second infection, whereas, if it is begun late, they are almost uniformly refractory to a second infection. It is suggested that this refractory state in rabbits may be explained by the existence of an acquired immunity which persists after the abolition of the disease rather than to the persistence of the first infection.

It would appear that it is possible under certain conditions to reinoculate rabbits and produce generalized infection without producing any lesion at the portal of entry.

AUTHORS' SUMMARY.

THE GREEN COLORATION BY CERTAIN STREPTOCOCCI ON BLOOD AGAR. WILLIAM A. HAGAN, J. Infect. Dis. **37**:1, 1925.

The formation of a green discoloration about the colonies of certain streptococci, and presumably of other green-forming bacteria when growing on blood agar, is due to the action on the blood corpuscles of peroxide and acid, substances which are produced simultaneously by these organisms when in the period of active multiplication.

The hemolysis which occurs about the periphery of the green zone when the period of incubation is prolonged, or when the plate culture is refrigerated while yet in an actively growing condition, is probably due to diffusing acid. Peroxide and acid have an antagonistic action on blood corpuscles, peroxide tending to discolor and protect them from hemolysis by the acid. Hemolysis results, therefore, only when peroxide production diminishes or ceases.

AUTHOR'S SUMMARY.

PROLIFERATIVE REACTION TO STIMULI BY THE LYTIC PRINCIPLE (BACTERIOPHAGE) AND ITS SIGNIFICANCE. PHILIP HADLEY, J. Infect. Dis. **37**:35, 1925.

Abnormally rapid growth (proliferation) is frequently observed in bacterial colonies under the influence of the lytic agent. Moreover, although such

proliferations may be regarded as analogous to those seen in the tissues of plants and animals experiencing an infection with an ultravirus, similar proliferation may also result from mechanical and chemical stimuli. The observations reported, therefore, while in harmony with d'Herelle's conception of the bacteriophage as an ultravirus, cannot serve as proof of this view.

The observations reported are also used as the point of departure for formulating certain modifications in d'Herelle's view which would make possible a correlation between his cases and a class of instances at present excluded by him from what he regards as the legitimate field of lytic action.

It is concluded that the phenomenon of transmissible bacterial autolysis is widespread in the bacterial world; and that although d'Herelle's hypothesis offers the easiest and most obvious explanation of the problem, we should not close our eyes to other possible avenues of approach.

AUTHOR'S SUMMARY.

STUDY OF YEASTS FROM HUMAN SOURCES. JANE F. PECKHAM, J. Infect. Dis. **37**:53, 1925.

Fifty-one cultures of yeasts from throat infections, bronchitis, stomatitis and vaginitis were identified. Forty-one of the cultures were pathogenic, producing abscesses in guinea-pigs; ten, nonpathogenic. One of the pathogenic yeasts, isolated from a throat culture and injected into animals, caused a lymphopenia; induced the formation of antibodies; was toxic in systemic effect; produced localized lesions characterized by necrosis, by infiltration of endothelial cells which fused to form giant cells and by a proliferation of fibroblastic tissue so marked in the pancreas that the islands of Langerhans were obliterated and glycosuria developed.

From the effect of yeasts on the blood and tissues of animals, it seems possible that they may become additional etiologic factors in infections caused primarily by other organisms. Yeast infections in guinea-pigs may be of service in the study of experimental diabetes.

AUTHOR'S SUMMARY.

THE USE OF RABBITS IN THE STUDY OF INFECTIOUS ABORTION. B. L. WARWICK, E. M. GILDOW and F. B. HADLEY, J. Infect. Dis. **37**:62, 1925.

Inoculation of rabbits is adaptable to the study of the abortion disease from several angles. It should prove of value in the study of immunity production. The typing of *Bacterium abortus* might be based on the results of inoculation of rabbits. The virulence of the organism under consideration can be quickly, definitely and economically determined. The virulence so determined should be more accurate and of more value than that determined by lesions produced as a result of guinea-pig inoculation. The variations in resistance to *Bacterium abortus* as shown by individual females of the same species suggests the probability of genetic differences in the germ plasm. Using this method of testing the females, it should be possible to determine whether strains of animals can be produced which are resistant to *Bacterium abortus*.

AUTHORS' SUMMARY.

BACTERIOLOGY OF ACUTE ILEOCOLITIS IN CHILDREN. R. CRUICKSHANK, Quart. J. Med. **72**:339, 1925.

B. dysenteriae of Flexner, Y type, was isolated from the stools in seven cases. In the convalescent stage of the illness, atypical dysentery bacilli were

isolated from the feces of four patients, and *B. Morgan* I from the feces of the other four. Since *B. dysenteriae* (Flexner) had previously been isolated from the stools of some of these cases, these types were regarded as concomitant bacilli rather than as the causal organisms. There is no conclusive evidence that organisms other than those of the *B. dysenteriae* group are primary infective agents in producing acute ileocolitis, although they may act as secondary factors in prolonging the diarrhea. *B. dysenteriae,* on the other hand, seems to produce an inflammatory condition of the large intestine and the lower part of the ileum, resulting in a type of diarrhea which is clinically distinguishable from acute infective gastroenteritis. The treatment suggested for acute ileocolitis in children is magnesium sulphate in repeated small doses every morning, together with antidysentery serum as a routine to combat the toxic symptoms.

J. A. M. A.

EFFECT OF FREEZING AND THAWING ON BACTERIOPHAGE. E. S. SANDERSON, Science **62**:377, 1925.

A bacteriophage for *Staphylococcus muscae* (Glasser), and another for a human strain of *Bacterium coli* were used. Heating at 60 C. for forty-five minutes inactivated the former, whereas the latter was only partially destroyed at this temperature.

One cubic centimeter quantities of the phages were frozen in small, sterile, cotton-plugged tubes on a freezing microtome with carbon dioxid gas. The cap of the freezing box was first unscrewed and the gas outlet covered with a piece of wire gauze to prevent the small tubes from resting in it. Over the small tubes was inverted a large test tube, four and one-half inches by one and one quarter inches, with a hole in the bottom of sufficient size to permit the escape of gas. Carbon dioxid freely expanding in this chamber quickly lowered the temperature to a point where solid carbon dioxid was produced, approximately —78 C.

The two phages were frozen and rapidly thawed ten, fifteen and twenty successive times, yet when titrated the titers never varied from those of control nonfrozen portions. Even when diluted ten thousand times with broth and then subjected to the freezing process fifteen times, no deleterious effect was to be noted on the staphylococcus phage.

By way of contrast, the following figures are given, indicating the numbers of a twenty-four hour old broth culture of *Bacterium coli* which failed to survive after the first, tenth and fifteenth freezing, respectively: 16 per cent, 86 per cent, 94 per cent.

The results would indicate the bacteriophage to be something other than a viable organism, unless it constitutes an exception to the generally accepted rule that repeated freezing-thawing is injurious to living cells.

VIRUS OF HERPES. ITS IMMUNE REACTIONS AND ITS RELATION TO THAT OF ENCEPHALITIS LETHARGICA. J. R. PERDRAU, Brit. J. Exper. Path. **6**:41, 1925.

The author isolated from spontaneous and recurrent herpes labialis types of virus which he designated as dermatropic and neurotropic, depending on their selective action. The neurotropic virus produced encephalitis in rabbits quite regularly when injected intracerebrally and in about 70 per cent of the

cases when applied to the nasal mucosa. The author calls attention to the fact that rabbits are subject to "spontaneous" encephalitis occurring in outbreaks suggestive of endemics, but he believes that the two forms can be distinguished by differences in the clinical course and the histologic changes in the nervous system. He believes that the results of this study were not influenced by spontaneously occurring encephalitis in the animals.

It is obvious that immunity against the neutropic virus cannot be produced by intracerebral or intranasal inoculations because of its great virulence by these routes. Intradermal inoculation, however, produces a cerebral immunity which is fully established in eleven days and lasts about three months. This period cannot be prolonged by repeated intracerebral inoculations. Application of the virus to scarified skin may produce a cerebral immunity, but occasionally it results in a fatal encephalitis, especially if the scratch is deep. The majority of animals which had had this temporary, and apparently local, cerebral immunity eventually succumb to intracerebral inoculations of the virus, and many show symptoms recalling those of epidemic (lethargic) encephalitis in man, and the virus cannot be recovered from the brain. The histologic changes in the brains of these animals are identical with those obtained from inoculation of emulsions of brain from cases of epidemic encephalitis.

L. A. HOAG.

THE VIRUS OF ENCEPHALITIS LETHARGICA. J. R. PERDRAU, Brit. J. Exper. Path. **6**:112, 1925.

Suspensions of brain tissue from patients dying of encephalitis have frequently been injected intracerebrally into rabbits in an attempt to isolate a specific virus. These attempts have often met with discouraging results. The author of this article recently reported the successful passage of herpes virus by intracerebral injections into rabbits which had been previously immunized against the virus, but in which the immunity had lapsed. He feels that during or after this temporary period of immunity a substance is formed which assists in the later successful implantation of the virus.

A similar technic was applied to the study of brain material from three fatal human cases of encephalitis, and from each was isolated a virus which could not be distinguished in its neurotropic properties from the herpes virus described in his previous paper. It was proved that the "aggressin" is not the virus itself.

L. A. HOAG.

CONTRIBUTION TO THE STUDY OF THE ETIOLOGY OF MUMPS. YVES KERMORGANT, Ann. de l'Inst. Pasteur **39**:565, 1925.

The organism described by Kermorgant is a spirochete cultivated from the saliva at the onset of mumps. Special anaerobic medium is necessary, and growth occurs only in symbiosis with a living gram-negative motile bacterium. During its evolution the spirochete forms granules which are filtrable, and this filtrate reproduces the original spirochete forms in the presence of the symbiotic organism. Inoculated in monkeys the spirochete determines a disease identical with human mumps. The filtered granular forms inoculated into the testicle of rabbit produce an orchitis similar to that produced by the whole culture. The serums after recovery from mumps contains specific agglutinins and lysins for the spirochete.

G. B. RHODES.

IMMUNITY TO TUBERCULOSIS OF THE BEE MITE. I. METALNIKOW, Ann. de l'Inst. Pasteur **39**:629, 1925.

Metalnikow's experiments demonstrate that the inability to infect the bee mite at any stage of its life and with any strain of the tubercle bacillus is due to phagocytosis. This progress is rapid, and the formation of giant cells and encapsulation comes from the same source. In the leukocytes the bacilli are digested and transformed into a brown-black pigment. This activity is not lessened during the critical period of metamorphosis when the leukocytes are most active in the process of transformation.

G. B. RHODES.

THE PFEIFFER BACILLUS AS CAUSATIVE AGENT IN CEREBROSPINAL MENINGITIS. EUGENE URECH and WALTER SCHNYDER, Ann. de l'Inst. Pasteur **39**:769, 1925.

In meningitis due to the Pfeiffer bacillus, Urech and Schnyder have found that the organisms in the spinal fluid are far from constant in morphology and cultural characteristics or serologic reactions. The virulence of strains from spinal fluids as well as from the throat or sputum also varies greatly.

G. B. RHODES.

REINFECTION IN EXTRAPULMONARY TUBERCULOSIS. A. AIDELSBURGER, Beitr. z. klin. Tuberk. **61**:138, 1925.

The author analyzed 331 protocols of necropsies performed in Aschoff's institute with the point in view to establish the immunizing effect which an extrapulmonary tuberculosis ("Organphthise") may have on the course of a later pulmonary infection. He found that the cases with an extrapulmonary focus were evenly distributed between productive and exudative pulmonary processes, whereas cases without extrapulmonary focus showed nine times as many exudative pulmonary processes as productive ones. Pulmonary tuberculosis was the cause of death in 13 per cent of the first group and in 65 per cent of the second group. The largest number of deaths occurred in the first group between 40 and 50 years of age; in the second group, between 20 and 30 years.

MAX PINNER.

THE MORPHOLOGY OF THE SPUTUM IN PULMONARY TUBERCULOSIS. M. SCHIELE, Beitr. z. Klin. Tuberk. **61**:187, 1925.

Schiele studied the cytology and the morphology of tubercle bacilli in sputum. She tends to the belief that the short bacilli are usually found in prognostically unfavorable cases. Phagocytosis was observed only in neutrophilic polymorphonuclear leukocytes. This cell type made up 76 to 99 per cent of the cells. Small and large mononuclear cells (lymphocytes?) were found up to 8 per cent, macrophages up to 21 per cent, eosinophilic leukocytes up to 7 per cent (completely missing only in cases *in extremis*). The more benign the case, the larger the percentage of mononuclears and macrophages. With clinical improvement a shifting toward the left in Arneth's count is observed. Increase of the percentage of phagocytized bacilli is found during clinical improvement.

MAX PINNER.

MATEFY'S SEROREACTION FOR THE DETERMINATION OF THE ACTIVITY OF A TUBERCULOUS PROCESS. A. SKUTETZKY, Ztschr. f. Tuberk. **43**:34, 1925.

Skutetzky found that this test permits one to judge the activity of a tuberculous process and that the degree of the reaction parallels the severity of the process. The test is unreliable for the diagnosis of incipient cases.

MAX PINNER.

PRIMARY TUBERCULOUS INFECTION OF THE CONJUNCTIVA. H. KUDLICH, Ztschr. f. Tuberk. **43**:66, 1925.

A girl, aged 4 years, showed tuberculous caseation in the parotideal, mandibular and cervical lymph glands. The site of the primary infection was found to have been in the conjunctiva, which at the time of necropsy was completely healed. The identity of the pathologic-anatomic changes in primary pulmonary and primary extrapulmonary infection is emphasized.

MAX PINNER.

PYORUBRIN, A RED WATER-SOLUBLE PIGMENT CHARACTERISTIC OF B. PYOCYANEUS. PERCY DAVOL MEADER, GEORGE H. ROBINSON and VEADOR LEONARD, Am. J. Hyg. **5**:682, 1925.

Typical strains of *B. pyocyaneus* produce fluorescent pigment, pyocyanin and pyorubrin, all water soluble. Freshly isolated strains from human lesions produce pyocyanin and pyorubrin abundantly and may be highly virulent, while old strains and strains from the environment may be powerless to produce anything else than the fluorescent pigment at the same time as they are avirulent. Virulent strains have a special affinity for the genito-urinary organs of laboratory animals.

SKIN SUSCEPTIBILITY TO TOXIC FILTRATES OF S. HAEMOLYTICUS SCARLATINAE IN CONVALESCENTS ACTIVELY IMMUNIZED AND NORMAL INDIVIDUALS. DONALD T. FRASER and A. H. GRAHAM, Studies from the Connaught Laboratories, Univ. Toronto **2**:2271, 1925.

The skin insusceptibility of scarlet fever patients to the toxic filtrate of *Streptococcus hemolyticus-scarlatinae* (Dick strains) rapidly increases during the course of the disease. The skin insusceptibility is a measure of immunity, the degree of which may be expressed in terms of skin test doses.

The negative reaction to 5 and 12½ skin test doses after the tenth day of illness is strong evidence of scarlet fever in a case of doubtful diagnosis which has given a positive reaction early in the disease. The degree of immunity in persons recovered from scarlet fever many years previously is comparable to that of recently recovered persons.

By active immunization a degree of skin insusceptibility to toxic filtrate may be produced comparable to that of persons recently recovered from scarlet fever. By passive immunization an immunity equivalent to two skin doses is rapidly produced in a high percentage of cases. Somewhat less than 50 per cent of passively immunized persons become positive to one skin dose within one month after the administration of antiserum.

PATHOGENICITY OF TRICHOMONAS INTESTINALIS. H. TSUCHIYA, Arch. Int. Med. **36**:174, 1925.

The observations on *Trichomonas intestinalis* lead to the conclusion that *Trichomonas hominis* is not a pathogenic but a harmless flagellate present in the large intestine. Constipation is a common occurrence in this disease. The intestinal flora is independent of the presence of *Trichomonas hominis* and does not alter the number of the flagellates.

S. A. LEVINSON.

ENZOOTIC DISEASES OF TURKEYS AND CANARIES CAUSED BY BACTERIA OF THE GROUP OF HEMORRHAGIC SEPTICEMIA (PARACHOLERA). A. BECK and W. HUCK, Centralbl. f. Bacteriol., Parasitenk. u. Infektionsk. I. O. **95**:330, 1925.

The authors isolated six strains of bacteria, five from turkeys and one from a canary, which were identical in all their reactions. They could be distinguished from the producers of bird cholera, rabbit and cat septicemia, and from the colon-typhoid group. They could be classed with the hemorrhagic septicemia group, in the type alpha of Plasaj and Pribram, that is, there were no flagella, no gas or indol formation, no coagulation of milk. In feeding experiments, the constant changes in canaries were enlargement of the liver and spleen with small places of focal necrosis. These are not found in *B. enteriditis* infections or in avian cholera, and seem to be specific for infections of the hemorrhagic septicemia type. In turkeys the changes were not as characteristic. The name "paracholera of turkeys" expresses well the clinical course, pathologic changes and relation to the group of hemorrhagic septicemia.

B. R. LOVETT.

Immunology

FIXATION REACTION APPLIED TO THE DIAGNOSIS OF TUBERCULOSIS IN DOMESTIC CARNIVOROUS ANIMALS. ACH URBAIN, Ann. de l'Inst. Pasteur **39**:764, 1925.

Urbain's experiments were made to determine the most satisfactory method of detecting tuberculosis in dogs and cats. The serums from fifty-nine cases of tuberculosis all gave a positive fixation reaction with a Besredha antigen; 97.15 per cent of healthy animals gave a negative reaction; only 62 per cent of the tuberculous animals gave a positive tuberculin reaction.

G. B. RHODES.

THE PRECIPITIN REACTION OF FIBRINOGEN. LUDVIG HEKTOEN and W. H. WELKER, J. A. M. A. **85**:434, 1925.

The fibrinogens of beef, chicken, dog, horse, human, sheep and swine blood are precipitinogenic. These mammalian fibrinogens, to which may be added those of the goat, guinea-pig, rabbit and rat, have antigenic elements or properties that are more or less common to all of them. Consequently, fibrinogen is not necessarily wholly different for each species, as seems to be the case with serum proteins and hemoglobin, but to a varying extent the same in different species, resembling in this respect casein, lens proteins, and to some extent thyroglobulin, and the principle of strict species-specificness does not hold in the precipitin reaction of mammalian fibrinogen. The specificness of chicken fibrinogen needs further study.

THE AGGLUTINATIVE CHANGES OF PNEUMOCOCCI IN THE ANIMAL BODY. TORU TAKAMI, Tohuko J. Exper. Med. **6**:248, 1925.

It has been noted by a number of investigators that pathogenic bacteria are changed both morphologically and biologically by passage through animals. The author found that avirulent pneumococci that were agglutinated by immune serum in 1:2,000 dilution, after passage through mice could be agglutinated only by 1:50 dilution. He concludes that variations of the original strains arise in the animal body which are no longer agglutinable by the original serum. This is due to the development of new receptors, as they can be agglutinated by serum obtained from animals immunized to the new strains. The virulence of bacteria and their agglutinability are in no direct relationship to each other. Strains developed from the same original culture by passage through animals of different species are different in their agglutination reactions. These facts should be kept in mind in preparing immune serums and vaccines and in differentiating various kinds of pneumococci by means of agglutination.

B. R. LOVETT.

SURFACE TENSION OF SERUM. XIV. CONCERNING THE CHANGE IN SURFACE TENSION OCCURRING AS A RESULT OF IMMUNIZATION. P. LECOMTE DU NOUY and LILLIAN E. BAKER, J. Exper. Med. **42**:9, 1925.

The nature of the relation between the time-drop and antibody formation cannot be stated as yet. It is certain that the physicochemical change in the serum, detected by means of surface tension measurements, is not due directly to the antibody itself. Neither is it due to the direct action of the antigen on the serum or to a change in the albumin-globulin ratio in the latter; rather does it appear like antibody formation itself to be due to a tissue activity. Further experiments are being carried out on this subject.

ON THE ANTIGENS OF RED BLOOD CORPUSCLES. II. FLOCCULATION REACTIONS WITH ALCOHOLIC EXTRACTS OF ERYTHROCYTES. K. LANDSTEINER and JAMES VAN DER SCHEER, J. Exper. Med. **42**:123, 1925.

Flocculation reactions of anti-erythrocyte serums on emulsions of alcoholic extract of blood are described. The reactions are markedly species-specific. Besides the homologous reactions, certain others — "heterogenetic" ones — have been observed, and in this way the existence of new examples of heterogenetic antibodies has been demonstrated.

Group-specific substances can be extracted from human erythrocytes with alcohol and demonstrated by flocculation with group-specific immune serum.

A conception of the structure of cellular antigens based on the known facts, is presented.

AUTHORS' SUMMARY.

STUDIES ON THE ANTIGENIC SUBSTANCE OF THE BACTERIAL CELL. HANS ZINSSER and TAKEO TAMIYA, J. Exper. Med. **42**:311, 1925.

The substance of the bacterial cell can be roughly divided into two antigenic entities. One of these is the so-called "nucleoprotein" substance, the other the residue substance or soluble material.

Immunization with the nucleoprotein is rendered free from bacterial bodies or fragments of bacterial bodies by Berkefeld filtration, incites the production

of only anticuleoprotein antibodies which, with slight group overlapping, are species-specific; but, as determined by the previous studies of Avery and subsequently those of Lancefield, they are not type specific to the same degree as the residue antibodies.

Immunization with dissolved residue alone leads to no antibody formation. This residue represents the haptophore group on which specificity depends, and which, in the simple process of solution, is disrupted from another substance together with which it represented a complete antigen in the antibody-forming sense.

The formation of specific antiresidue antibodies is apparently dependent on the injection of morphologically formed elements, at least as far as experiment can determine at the present time; for, as in the pneumococcus experiments, the most available process of solution and the injection of all the materials so obtained from the whole bacteria fails to yield antiresidue antibodies, as though in the mere process of dissolving the residue haptophore group was dissociated from its association with the larger molecule to which in the whole bacteria it lends specificity.

While antiresidue antibodies are formed only when such undisrupted bacterial cell substances are present in the immunizing substance, immunization with whole bacteria, even when attempts are made to preserve them from solution by liquor formaldehydi, leads to the formation of both antiresidue and antinucleoprotein antibodies, probably because a certain amount of solution inevitably takes place after injection within the animal body.

AUTHORS' SUMMARY.

THE ANTIGENIC PROPERTIES OF TISSUE FIBRINOGEN. CORNELIA M. DOWNS, J. Infect. Dis. **37**:49, 1925.

A protein which is an active blood coagulant and which has antigenic properties distinct from the serum antigens can be precipitated from lung extracts. Proteins that are chemically and antigenically identical with the lung protein can be isolated from liver and kidney extracts. These proteins show species specificity in their antigenic properties but not in their action in blood clotting.

AUTHOR'S SUMMARY.

ANTIGENIC PROPERTIES OF LYSOZYME-DISSOLVED VACCINES. V. D. ALLISON, Brit. J. Exper. Path. **6**:99, 1925.

Lysozyme is a bacteriolytic substance which has been shown by Fleming and Allison to be present in practically all the secretions and tissues of the human and animal body. The author used the lysozyme of human tears to prepare a vaccine of dissolved *Streptococcus fecalis* in order to compare its antigenic properties with those of a heat-killed, saline suspension of the same organism. Intravenous injections of both preparations were given to the rabbits at weekly intervals, and a study was made of the immunologic reactions of the serum against *Streptococcus fecalis*.

The animals receiving the dissolved vaccine showed a well marked increase in bactericidal power, as evident as that resulting from the use of heat-killed vaccine, and a formation of specific complement-fixing substances. There was little rise in opsonic power and none in the bacteriolytic and agglutinating properties. This was in contrast to the increase in the latter properties following the injection of heat-killed vaccine.

These results are in general agreement with those of Douglas who studied vaccines in which the organisms had been digested with trypsin.

L. A. Hoag.

Action of Alkaloids on Formation of Agglutinins. P. Butiagin, Prophylakt. Med. **4**:11, 1925.

Experiments were made on rabbits, using typhoid bacilli as antigen. Repeated injections of pilocarpin appeared to increase the amount of agglutinin; cocain also seemed to stimulate production, but eserin, atropin and pituitary extract were without effect.

Precipitin Production Through Lens Injury. M. F. Guyer, J. Infect. Dis. **37**:93, 1925.

The blood of rabbits that have previously given negative precipitin reactions to lens often show lens precipitins within from seven to ten days after needling the lens in situ. In rabbits with hereditary cataract, lens antibodies in the form of precipitin is present in some cases, at least, in the blood serum; lens antigen probably is not.

Precipitin Reaction of Thyroglobulin. Ludvig Hektoen and Kamil Schulhof, Proc. Nat. Acad. Sc. **11**:481 (Aug.) 1925.

Thyroglobulin precipitins appear to be specific for thyroglobulin but are not consistently species-specific; thyroglobulin is present as such in the colloid of the thyroid gland; the rabbit can produce precipitin for rabbit thyroglobulin; thyroglobulin may occur in the blood from the human thyroid vein; the precipitin test does not indicate any difference between thyroglobulin from the normal thyroid and that from exophthalmic goiter; the fetal human thyroid contains thyroglobulin in the third and fourth months, if not earlier.

The Formation of Antibodies to Sheep Blood in Experimental Tuberculosis of Rabbits. Ludvig Hektoen and H. J. Corper, J. Infect. Dis. **37**:82, 1925.

A rapidly fatal general tuberculosis in the rabbit from the intravenous injection of virulent bovine tubercle bacilli was without definite effect on the agglutinin and lysin content of the serum even to within a few days of death, while precipitin formation seemed to be slightly retarded.

Local subcutaneous tuberculosis in rabbits produced by the injection of avirulent human tubercle bacilli ten and twenty-six days before the intraperitoneal injection of sheep blood had no appreciable effect on lysin or precipitin formation, but two of the rabbits given sheep blood forty-three days after infection maintained high specific lysin and precipitin titers for two hundred and four hundred and forty-five days.

Whether the tuberculosis was the cause of the unusual reaction of these two rabbits has not been determined, but the results are similar to those that Lewis and Loomis obtained in tuberculous guinea-pigs.

Rabbits infected subcutaneously with avirulent human tubercle bacilli and given sheep blood intravenously at different intervals after infection revealed slight variations in antibody formation from the usual course.

Tuberculosis in the rabbit, either general or local, apparently has no marked influence on the antibodies that develop from the injection of sheep blood. In exceptional cases, it may result in a prolongation of antibody accumulation in the blood.

AUTHORS' SUMMARY.

RIECKENBERG'S PHENOMENON AND ITS USE IN IMMUNITY INVESTIGATIONS. A. M. BRUSSIN and W. K. BELETZKY, Centralbl. f. Bakteriol., Parasitenk. u. Infectionsk. I. O. **96**:32, 1925.

When the blood of a mouse that has received injections with a trypanosome is mixed in citrate broth with the blood of a mouse immune to the same trypanosome, the blood platelets of the immune animal become attached to the organisms. This reaction is highly specific for the strain of trypanosomes used. The same mouse can have at the same time a number of antibodies for different kinds of trypanosomes. The reaction can be used to separate different strains of organisms, to investigate the immunity in trypanosome infections, and to demonstrate the changes which the organisms undergo in the course of an infection. Its extraordinary sensitiveness is somewhat of a hindrance, however, in its practical application.

B. R. LOVETT.

CONCERNING THE EXISTENCE OF CELLULAR ANAPHYLAXIS. I. ACTIVE CELLULAR ANAPHYIAXIS IN DOGS. I. L. KRITSCHEWSKY and K. A. FRIEDE, Centralbl. f. Bakteriol., Parasitenk. u. Infektionsk. I. O. **96**:56, 1925.

Cellular anaphylaxis against erythrocytes can be demonstrated in dogs. All dogs that we used had anaphylactic shock. In most cases they were hypersusceptible after one injection; three dogs had to be sensitized twice. Some had only one anaphylactic shock, others several. The more severe the shock, the more antibodies (hemolysins) were present in the dog's serum. The symptoms of shock in cellular anaphylaxis resemble those in serum anaphylaxis.

B. R. LOVETT.

Tumors

PRIMARY LYMPHOSARCOMA OF THE PAROTID. V. EFREMOW, Beitr. z. path. Anat. u. z. allg. Path. **73**:486, 1925.

To five previously reported small round cell sarcomas of the parotid, Efremow adds a primary lymphosarcoma of the parotid in a 27 year old man.

O. T. SCHULTZ.

CONTRIBUTION TO TUMOR PATHOLOGY. 1. THE GENESIS OF TERATOMA DIPHYLLICCUM. 2. DURAL IMPLANTATION OF METASTASES IN NEUROMA OF CEREBELLOPONTINE ANGLE. A. SCHMINKE, Beitr. z. path. Anat. u. z. allg. Path. **73**:502, 1925.

In a 12 day old child congenital malformation of the left lower extremity was associated with multiple internal maldevelopments and a teratomatous tumor composed of entodermal derivatives and neurogenous tissues. Schminke believes that the tumor arose as the result of the same mechanical factor that caused the developmental anomalies and that it could not have arisen from a

totipotent blastomere. The bilateral acusticus tumor described was unusual in that it was a neurinoma, not an endothelioma or psammoma. Multiple small dural tumors present were believed to have arisen by implantation.

O. T. SCHULTZ.

TUMORS OF LATERAL ABBERRANT THYROIDS. A. E. BILLINGS and J. R. PAUL, Bull. Ayer Clin. Lab. Pennsylvania Hosp. **9**:27, 1925.

A case of papillary adenocarcinoma of a lateral aberrant thyroid gland is reported, together with thirty-four other cases of tumors of lateral aberrant thyroids which have been collected from the literature.

The pronounced tendency of the lateral aberrant thyroids to give rise to papillary adenoma and adenocarcinoma is noted, and emphasis is laid on the difference in behavior of the lateral thyroids in this respect from that of median or lingual types of aberrant thyroids which seldom give rise to malignant tumor formation.

IMMUNITY IN CANCER. FRANCIS CARTER WOOD, J. A. M. A. **85**:1039, 1925.

The conclusions are that there is no evidence that the infrequent spontaneous regressions of human tumors are due to any process of immunization; further, that there is no evidence that the similar spontaneous disappearance of primary animal tumors is due to any process of immunization. The spontaneous regressions, so ofter observed in transplanted animal tumors, are looked on as an entirely different phenomenon. The tumor is a graft into a healthy host and hence is not perfectly adapted to the soil. There is no cogent evidence for, and much against, the conclusion that any process of immunization aids in the therapeutic efficacy of irradiation. Clinical cures can sometimes be obtained by irradiation in situations in which complete tumor cell destruction is impossible but extensive connective tissue sclerosis can be produced, thus locking up any viable cells. The production of absolute permanence of cure by radiation therapy implies that the destruction of the tumor cells must be as complete as must be their removal for effective surgery.

EFFECT OF PREPUBERTY CASTRATION ON SUBSEQUENT CANCER IMPLANTATION. JAMES B. MURPHY and ERNEST STURM, J. Exper. Med. **42**:155, 1925.

Male and female mice castrated during the first seven weeks of life and implanted with cancer at later periods show a resistance definitely higher than do intact animals of the same age. This increased refractiveness is evident three months after the operation but is more pronounced in eight months to a year after operation. Even castration in early adult life seems to increase the refractory state to later cancer inoculation. On the other hand, adult mice inoculated within a week after castration show slight if any evidence of increased resistance.

AUTHORS' SUMMARY.

EXPERIMENTS ON CANCER PRODUCING SUBSTANCES. E. L. KENNAWAY, Brit. M. J. **2**:1, 1925.

Further experiments on the formation by heat of cancer producing materials are described by Kennaway. The nine products tested were obtained from the following sources at approximately the temperatures stated: acetylene (700, 800 and 900 C.); California petroleum (880 C.); isoprene (700 C.); Durham Holmside coal (450, 560 and 1,250 C.); human skin (290 C.); yeast

(290 C.). It is stated that the pyrogenous materials derived from acetylene isoprene, petroleum yeast and skin produce cancer simply because they are all "irritants"; and that the multiplication in the laboratory of instances of "chronic irritation" is not required. To apply this to a substance, after it has been shown to produce cancer, the term "irritant" gives an appearance of explanation which is illusory. There seems to be a tendency present to state that a substance such as soot gives rise to cancer because it is an irritant, and at the same time tacitly to regard it simply as an irritant because it gives rise to cancer; this circular treatment of the matter is of no value. The irritation which causes the growth of cancer must be a special kind or must act on some special element in the tissues. No invariable relation has been found between the temperature at which these various materials are formed and their comparative activity in producing tumors. Thus the three tars made from coal at 450 C., 560 C. and 1,250 C. show an ascending order of potency; the 820 C. isoprene tar is more active than the 700 C. tar; and experiments still in progress indicate that the 920 C. tar will prove more effectual than the 780 C. tar. In all these cases the higher temperature gives the more active produce; but, on the other hand, in the case of acetylene, a low temperature (700 C.) gives a product more active than that produced at from 800 to 900 C. The idea suggests itself that acetylene may be a decomposition product common to coal, mineral oils, yeast, skin and isoprene, and that the cancer producing material obtained from these diverse sources is actually formed from acetylene by the synthetic process discovered by Berthelot. Probably the yield of cancer producing substance depends largely on catalytic reactions which cannot as yet be controlled.

ARCH. DERMAT. & SYPH.

EXPERIMENTAL TREATMENT OF IMPLANTED MALIGNANT TUMOR OF RAT. T. LUMSDEN, Lancet **2**:539, 1925.

The tumors employed by Lumsden in this study were the mouse carcinoma (M. 63 of the Imperial Cancer Research Laboratory) and Jensen's rat sarcoma. In most cases the sarcoma was used because it was found that while M. 63 is satisfactory for in vitro work, it is less suitable for experiments in vivo. It appears that an appropriate antiserum kills cancer or sarcoma cells in vitro, rapidly and invariably. It is much less toxic to the normal tissues than to the malignant cells. Pieces of cancer tissue kept in antiserum for from three to six days at 37 C. do not thereafter produce a progressive tumor when inoculated into the living animal. Jensen's rat sarcoma of the foot can be caused to disappear by repeated injections of antiserum into and round the tumor, along with temporary stoppage of circulation in the foot. After such removal of a tumor the rat becomes immune, so that a subsequent inoculation of Jensen's rat sarcoma into the other foot or into the axilla does not hold. When an implanted tumor is growing on each foot, removal of one of these by means of antiserum and constriction is, in a large proportion of cases, followed by absorption of the tumor in the other untreated foot. It is suggested that during absorption of the tumor after treatment with antiserum and constriction, the products absorbed from the attenuated or dying cells evoke a general active immunity which completes the cure and prevents subsequent grafts from holding. Such an antiserum might in this way prevent recurrence of a tumor after incomplete surgical removal.

J. A. M. A.

CANCER AMONG NATIVES OF SOUTH AFRICA. N. MACVICAR, South African M. Rec. **23**:315, 1925.

Among 10,000 inpatients coming from South African natives, Macvicar found ninety-seven cases of carcinoma, thirty cases of sarcoma, fourteen cases of internal growths — brain, chest, abdomen — of obscure nature but probably malignant. Cancer of the mouth seems to be rather common. Macvicar attributes it to the irritation of the things many native men and women carry in their mouths, especially plugs of coarse tobacco, possibly also to the long wooden pipes they use. Cancer of the liver is common in comparatively young men, and even boys. It seems to be due to schistosome infection. Cancer of the breast is rare. Macvicar is inclined to attribute this immunity to the fact that in their natural state Bantu women do not wear corsets, and rarely do so even when adopting other European clothing. The few who did wear the high ribbed corset of the last generation seem to have suffered from cancer as commonly as Europeans.

J. A. M. A.

COURSE OF EPITHELIAL CHANGES IN TAR TUMORS OF RABBITS. MARJA WILHELMI, Trav. d'Inst. d'anat. path. d. Univ. de Pologne **1**:217, 1925.

Five stages are described following the painting of the rabbit's ear with tar: First, a general hypertrophy occurred, with thickening of the epithelium and hyperkeratosis. Then nodules formed, composed either of thickened hair follicles, follicular epitheliomas or of squamous epithelial cells, papillomas. Many of the growths remained in this stage, but some went on to the precancerous stage, in which the cells showed beginning malignant changes. The fourth stage of true cancer occurred at the earliest at the end of five months. The epithelial cells invaded the underlying tissues, and were found frequently in isolated groups. Mitotic figures were frequent. In the fifth stage, of regression, the benign growths disappeared or took on the character of epithelial horns and fell off. Even the cancerous growths underwent regression after the tar painting was stopped. This fact, with the absence of metastases and the lack of invasion of the cartilage by epithelial cells, indicates that the growths are less malignant than cancers in man. One must be cautious in drawing conclusions concerning human cancers from tar growths in animals.

B. R. LOVETT.

CONCERNING THE FREQUENCY OF BRONCHIAL CANCER. HEDWIG HOLZER, Med. Klin. **21**:1235, 1925.

According to reports from several sources, there appears to be an increased number of cases of bronchial cancer in central Europe. Holzer presents figures showing a marked increase in bronchial cancer since about 1919 in the necropsies in the German Pathologic Anatomic Institute in Prague. In fact, the percentage of bronchial cancer in the total number of cases of cancer generally appears to have increased about 300 per cent. All the various forms of bronchial cancer were encountered. The causes of this increase are not known.

A CASE OF CARCINOMA OF THE APPENDIX (WITH SPECIAL CONSIDERATION OF THE ARGENTAFFINE GRANULES). WERNER V. REHREN, Centralbl. f. allg. Path. u. path. Anat. **36**:355, 1925.

A carcinoma of the appendix is described with unusually numerous metastases. Argentaffine granules were found in both primary and secondary

growths. In a case of ovarian carcinoma with similar metastases, no granules were found in the cells. It seems, therefore, that the presence of the granules is not only evidence for the histogenesis of intestinal carcinomas from the "cells of Kultschitzky," but also a help in the differential diagnosis of the primary tumor.

B. R. Lovett.

The Action of Oils in the Production of Tumors. M. T. Burrows and C. G. Johnston, Arch. Int. Med. **36**:293, 1925.

Burrows and Johnston by experiments on animals with oils and coal tar products have shown that they act to build a dense, stagnant mass of cells by drawing the tissue cells to them and away from their intercellular substances and blood vessels. The authors assert that cancer is an independent growth of cells and may be induced by any one of a number of conditions and substances, and when once established proceeds independently of the causative agents. Bacteria may induce cancer in the same manner by building a densely cellular stagnant mass of cells, stimulating the cells of the tissue to proliferate without to any extent forming intercellular substances and blood vessels. Stagnation and cell crowding become important for growth because it depends on a certain concentration of a primary product of the oxidation of the cells, the archusia. The functioning organism is evidently the result of an environment rich in growth stimulating substances supplied by preexisting lower growing and nonfunctioning forms. In cancer the cell becomes independent. Any tissue may be made cancerous by anything that frees the cells from the effect of their intercellular substances and an active circulation of blood.

S. A. Levinson.

A Lipoma of the Third Ventricle. H. A. Woelk, Centralbl. f. allg. Path. u. path. Anat. **36**:357, 1925.

An egg-sized lipoma was found nearly filling the third ventricle. It was attached to, and probably arose from, the tela choroidea of the third ventricle. No symptoms of brain tumor were recognized during life.

B. R. Lovett.

Medicolegal Pathology

The Presence Post Mortem of Nitric-Oxide Haemoglobin: Its Clinical and Medico-Legal Significance. H. A. L. Banham, J. S. Haldane and Thomas Savage, Brit. M. J. **2**:187, 1925.

A case is described in which postmortem appearances simulating closely those of carbon monoxide poisoning were found to be due probably to the formation after death of nitric oxide hemoglobin. The patient, a stoker, became ill on the way home; respiratory symptoms developed, and death took place nine days later. Necropsy showed patches of pneumonia. The blood as well as the internal organs were red and pink. It has been shown by Haldane and others that animals killed after receiving a dose of nitrite have a bright red blood after death, and the possibility of this being mistaken for carbon oxide hemoglobin was pointed out by them in 1897. In the case now reported it is suggested that as the red color of the blood could not be due to carbon monoxide it may have concerned the formation of nitric oxide hemoglobin from the

activity of a nitrifying microbe in the lungs or elsewhere within the body. One of the authors (Banham) observed during the war that after death from influenzal pneumonia the blood frequently was cherry red. The possible presence of nitric oxid hemoglobin should be considered in cases of suspected carbon monoxide poisoning. "The distinction can be made with great ease by boiling a watery solution of the blood. If the red color and other corresponding chemical reactions or spectroscopic appearances are due to NO-haemoglobin the coagulum will be pink. No other simple test at present known appears to be reliable for distinguishing CO-haemoglobin from NO-haemoglobin."

METHOD FOR DETERMINATION OF DEATH BY DROWNING. A. PALMER and W. M. DOHERTY, M. J. Australia **2**:103, 1925.

Of six cases of drowning in sea water five showed a definite increase of chlorids in the blood of the left side ranging from 25 to 23. In the sixth case, it was present in equal amounts on the two sides. It is suggested that a patent foramen ovale was missed at the necropsy.

THE RÔLE OF BRAIN CONCUSSION IN FATAL SKULL INJURIES. KARL MEIXNER, Deutsch. Ztschr. f. ges. gericht. Med. **6**:105, 1925.

From conditions found in the brains of sixty-nine persons dying from head injuries and examined in Haberda's Institute in Vienna, Meixner concludes that concussion alone never causes death, and that when it contributes to death, concussion or compression or both play a larger rôle. He comments on the tendency during recent years to adopt this view and cites others who support it, a view in considerable contrast to that held regarding cerebral concussion some years ago.

No mention is made of microscopic examination of the brains, and had this been done, the importance of contusions — minute traumatic hemorrhages — would have been still greater.

E. R. LE COUNT.

FORMALDEHYD POISONING. B. S. KLINE, Arch. Int. Med. **36**:220, 1925.

Of the twelve fatal cases, ten came to necropsy. In all these, the changes were most marked in the lower esophagus and to an even greater extent in the stomach. The changes in these organs varied from simple hardening of the tissues to extreme corrosion. Frequently, marked congestion and edema were present, with areas of erosion and of hemorrhage. Occasionally similar but less marked changes were observed in the duodenum and even jejunum. The remainder of the alimentary canal rarely showed any abnormality. In cases continuing thirteen hours or longer after ingestion of the formaldehyd, degenerative changes in the parenchymatous organs were noted, varying from slight cloudy swelling to fatty degeneration and even patchy necrosis. In a few cases the blood was still fluid and was dark red at the time of the necropsy. One case of sixty-two hours' duration showed 200 cc. of purulent exudate in the abdominal cavity. In this case there was considerable involvement of the stomach with inflammatory changes reaching to the serosa. In one case death was apparently due to diffuse bronchopneumonia. In a few others, there was a terminal pulmonary edema. In one case the changes were practically limited to the respiratory tract as far as the bifurcation of the trachea.

AUTHOR'S SUMMARY.

Technical

TECHNIC FOR CULTIVATION OF ANAEROBES. VERCELLANA, Pathologica **17**:410, 1925.

Vercellana has modified Rockwell's pyrogallic acid method. Instead of pouring the acid on the cotton plugging the tube with the culture — which has certain disadvantages — he puts the pyrogallic acid in an Erlenmeyer jar below the culture. The agar is poured into a bottle to form a thin coating throughout the bottom of the bottle. This is inoculated with the microorganism; the flask is then inverted, and the mouth is introduced into the mouth of the Erlenmeyer jar. The junction is made air-tight with shellac. He has cultivated in this way the bacillus of tetanus and of malignant edema, using in the jar 50 cc. of a 10 per cent solution of potassium hydrate and 5 gm. of pyrogallic acid, instead of Rockwell's mixture. Two test tubes can be used in the same way, shellacking the two mouths together. They can be separated by holding the shellac over a flame.

J. A. M. A.

COMPARISON OF GOLD CHLORID, BENZOIN AND MASTIC TESTS ON CEREBROSPINAL FLUID. J. R. COCKRILL, Arch. Neurol. & Psychiat. **14**:455 (Oct.) 1925.

Four hundred colloidal — gold, benzoin and mastic — tests show sixteen dissimilar reactions and 384 similar reactions in all three tests. Comparing the colloidal benzoin and mastic with the colloidal gold, the results indicate that the benzoin and mastic are reliable tests of approximately equal value. The technic of the benzoin is simpler. This indicates that the benzoin is the colloidal test to use in the routine examination of cerebrospinal fluid. In special cases, such as meningitis and multiple sclerosis, requiring the original benzoin test of sixteen tubes, the colloidal gold test is preferable.

AUTHOR'S SUMMARY.

A MICRO-FOLIN-WU METHOD OF QUANTITATIVE BLOOD-SUGAR ESTIMATION. T. L. BYRD, J. Lab. & Clin. Med. **11**:67, 1925.

The author uses a blood diluting pipet, graduated at 0.1 cc. and 0.8 cc., with two chambers, the first having a capillary intake expanding into a fusiform shape of 0.1 capacity for obtaining and measuring the blood, the second, having 0.7 cc. capacity for diluting, mixing and laking, with constrictions of the bore at each graduation. This pipet solves the problem of obtaining blood from patients in small quantities. A rubber band placed over the ends of the pipet after the blood is drawn and diluted makes it possible to carry it about without loss. The blood can be diluted with 1:400 formaldehyde solution in place of distilled water, thus preserving the blood for several days without change of the sugar content. The Folin sugar tubes are reduced to one quarter the usual size. This is a simple and accurately minimized Folin-Wu method, which obviates the necessity of puncturing the vein in order to obtain blood.

A METHOD FOR RAPID DIAGNOSIS OF PERNICIOUS ANEMIA. F. E. LOWY, Klin. Wchnschr. **4**:828, 1925.

A smear of suspected blood is superimposed on a stained smear of normal blood. The comparative difference in size of the red cells is striking. According to Naegeli, megalocytosis is a constant finding, even in the earliest forms of pernicious anemia, and is also present in the remissions.

Lowy also regards the method as a diagnostic aid in constitutional hemolytic icterus when the anisomicrocytosis gives similar comparative information.

A. B. SCHWARTZ.

CONTRIBUTION TO THE STUDY OF THE VAN DEN BERGH REACTION: ITS MECHANISM AND VALUE IN THE CLASSIFICATION OF ICTERUS. GIOVANNI FAVILLIE, Sperimentale **79**:647, 1925.

The diazo reaction is the most precise and sensitive method for detecting bilirubin in the blood, but it is not possible by means of this test to discriminate the two principal types of icterus.

LEUKEMIA. M. N. RICHTER, Arch. Int. Med. **36**:13, 1925.

The peroxydase reaction in leukemia is of less value in diagnosis than the study of stained smears and is of no value in differentiating hemocytoblasts in cases of myeloid leukemia from those of lymphoid leukemia.

Leukocytic peroxydases demonstrable in blood smears by the benzidin method described by the author occur only in leukocytes that contain granules of one of the following types: (*a*) neutrophilic; (*b*) eosinophilic; (*c*) azurophilic granules of monocytes, and (*d*) azurophilic granules of the myeloblasts of Ferrata (promyelocytes of Naegeli), including Auer bodies.

Leukocytes totally devoid of granules do not react for peroxydases. Elements containing the following types of granules do not react: (*a*) basophilic, (*b*) basophilic (immature) granules of eosinophil myelocytes, (*c*) azure granules of lymphocytes, and (*d*) granules of platelets and megakaryocytes.

The azurophilic granules of myeloid cells (myeloblasts of Ferrata) probably represent an early stage of myeloid transformation of the hemocytoblast.

S. A. LEVINSON.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Oct. 12, 1925

RUTH TUNNICLIFF, M.D., *President, in the Chair*

A DIPLOCOCCUS IN MEASLES. Presidential address by DR. RUTH TUNNICLIFF.

The scientific investigation of the etiology of measles began with the experiments of Dr. Hektoen in 1905. He produced the disease in man by the injection of blood drawn from patients with measles early in the disease, thus showing that the virus was present in the blood. Anderson and Goldberger later demonstrated that monkeys were susceptible to measles materials collected just before or early in the eruptive stage and that the virus passed through a Berkefeld filter. Later Nevin and Bittman found that rabbits, and Duval and D'Aunoy that guinea-pigs, reacted to the injection of measles virus. After a fairly definite incubation period depending on the method of inoculation of blood or washings from the nose and throat from patients with measles, monkeys and rabbits develop leukopenia, rise of temperature, Koplik spots and an eruption, followed by desquamation. Guinea-pigs show only a fall in the number of leukocytes, a rise of temperature and, according to Duval and D'Aunoy, a hemorrhagic nephritis. Respiratory symptoms are generally absent in the measles reaction of lower animals.

Since the aerobic blood cultures on ordinary mediums made by earlier investigators failed to demonstrate bacteria, I tried anaerobic cultures in special mediums, such as semicoagulated horse serum and ascites agar. During the preeruptive and early eruptive stage of measles, a filter passing gram-positive, green producing diplococcus was found almost constantly in the blood. It never grew in the first generation in fluid mediums, probably because they are more aerobic than solid or semisolid ones. This diplococcus was isolated in largest numbers a few hours before the appearance of the eruption. After the first generation it generally grew aerobically. The same diplococcus has been found constantly in smear preparations and cultures from the respiratory tract during the same period it was found in the blood. Specific agglutinins, opsonins and complement-fixing bodies for this coccus have been demonstrated in the blood of patients with measles as the symptoms subsided. By means of immune rabbit serum the strains of this organism from measles have been shown to belong to one biologic group. This coccus has not been found in the blood in other diseases or in normal blood.

The same symptoms and lesions produced in monkeys, rabbits and guinea-pigs by infectious measles material appeared also to be caused by this organism, because other bacteria isolated from the same plates failed to produce the measles reactions. Rabbits successfully inoculated with this measles coccus showed no reaction when reinoculated with fresh measles material. The coccus isolated from the blood and lungs of rabbits inoculated with the measles coccus also produced a rise of temperature, Koplik spots and rashes when injected into normal rabbits.

I have also studied the skin reactions to this diplococcus with a view to obtaining light on its relation to measles. Filtrates of cultures failed to produce any reaction. The most satisfactory reaction was obtained by the intracutaneous injection of 0.2 c.c. of a twenty-four hour anaerobic ascites dextrose broth culture, killed by 0.5 per cent. phenol at room temperature. Knowing that rashes could be produced in rabbits by this coccus, I first made tests in the skin of shaved rabbits. Normal rabbits reacted with circumscribed, indurated, red areas from 1 to 4 cm. in diameter within twenty-four hours after injection. Rabbits immune to measles showed no reaction to the measles antigen. Twenty-one strains of bile insoluble, green producing diplococci were then tested. The six measles strains gave marked reactions in normal rabbits, but none in rabbits immune to measles. Four strains from other sources gave reactions in rabbits both immune and not immune to measles. The other strains failed to produce any reactions.

The serum of goats and a rabbit immunized with this diplococcus, as well as convalescent human measles serum neutralized the measles antigens, but normal goat and rabbit serums failed to do so. Convalescent human measles serum did not neutralize the coccus antigens not derived from measles.

Similar tests were made in human beings with two different measles antigens. The antigen was diluted with salt solution to a point that gave no reaction in persons who had previously had measles. No reaction occurred with the control culture mediums except sometimes a redness 0.3 cm. in diameter at the site of the needle prick. Twenty-eight persons who gave a history of measles or were convalescing from measles showed no reaction. One person with a history of measles reacted positively. Twenty-six persons who had not had measles gave a definite reaction generally in twenty-four hours, in the form of a circumscribed area of erythema of varying intensity from 1 to 2 cm. in diameter, as a rule with slight infiltration. The reaction in some instances was followed by pigmentation and desquamation and generally disappeared in twenty-four hours. The serum of a person with a negative history of measles who gave a positive skin reaction failed to neutralize while convalescent human measles serum did neutralize the measles antigen when injected into persons who had not had measles.

Since these experiments suggested that this diplococcus might be peculiar to measles, it seemed worth while to try to produce immune serum in a large animal for preventive inoculations. Others have shown that monkeys, guinea-pigs and rabbits recovering from measles produced experimentally with measles virus are immune to reinfection. Scott and Simon also showed that the blood of rabbits infected with measles virus will protect uninoculated rabbits when later infected with measles material.

Nicolle and Conseil, Degkwitz, McNeal, Weaver and Crooks, Zingher and others have proved the protective power of convalescent measles serum against measles. Since monkeys, guinea-pigs and rabbits were found susceptible to the green producing diplococcus isolated from measles patients, it seemed possible that a goat might also react to this organism, and if so the blood drawn during convalescence might show protective power against measles. A goat was chosen rather than a horse on account of the danger of sensitization with horse serum if used in other diseases and also on account of the common belief that goat serum is not toxic to man.

From nine to fourteen days after intravenous injection of living measles diplococci, goats showed a rise in temperature, a leukopenia and congestion of the mucous membrane of the mouth. Blood drawn during convalescence

neutralized measles antigens when injected intracutaneously into rabbits, and protected ten rabbits against a subsequent injection of infective material from measles. The six rabbits receiving injections with normal goat serum or uninoculated before receiving the measles virus all showed some or all of the characteristics of measles in rabbits: a rise of temperature, Koplik spots and an eruption.

On account of the difficulty of always obtaining convalescent human measles serum and the indication that immune goat serum protected rabbits against measles, Dr. Hoyne and I have tried immune goat serum in a few children who had not had measles, convalescent human serum collected by Dr. T. T. Crooks being used as a control.

Of the sixteen children with a negative history of measles receiving goat serum on the first two days after exposure, twelve showed no signs of measles. Six children receiving the serum on the third day or later, developed measles. In the cases in which human convalescent measles serum was used as a control the percentage of persons who contracted measles was the same as in those receiving injections with goat serum. A number of other children also received goat serum but were later found not to have been exposed to measles.

The serum of one goat was toxic to fifteen of the twenty-three children receiving injections. It is possible that if the serum was concentrated and preserved for a longer time before using, some of the toxic effect might be avoided.

While too few experiments have been made to draw any conclusions as to the protective value of immune goat serum, we think they warrant further investigation, especially with serum of goats more highly immunized.

The coccus in pairs and short chains observed by Babes in 1880 in the secretions from the nose, conjunctiva and bronchi of patients who had measles, the diplostreptococcus isolated from the sputum by Menschikow, the gram-positive coccoid bodies seen by Mallory and Medlar in the skin and the green coccus isolated by Donges from the blood in measles may be the same coccus which I have cultivated. It is interesting that Menschikow suggested that his coccus might have the same relation to measles that the hemolytic streptococcus had to scarlet fever. The filter-passing diplococcus recently isolated by Caronia from measles differs from my organism in being gram-negative and always anaerobic. The ascites tissue medium used by him is unfavorable for the growth of my diplococcus, and after several generations they become almost invisible, and many become gram-negative. Caronia isolated the coccus he describes not only from measles material, but also from the blood of rabbits inoculated with blood from patients with measles. Selma Meyer, who worked with Caronia and studied his technic, reports that bodies like those described by him as the cause of measles and scarlet fever were found by her also in uninoculated culture mediums and in blood cultures from chickenpox, chorea, polyarthritis and other diseases, as well as from normal blood. Rabbits receiving injections with uninoculated culture medium showed bodies in the liver and spleen like those in rabbits receiving injections with blood from patients who had scarlet fever and measles.

At the height of the attack of measles, gram-positive bacilli and other organisms were sometimes isolated from the blood, but as I did not find them in the preeruptive stage, when the blood is known to be infective, and as no opsonins, agglutinins or complement-fixing bodies could be demonstrated for them, they were not considered to be of any etiologic significance. Some of

these bacilli may be the same as those isolated by Sellards and Bigelow from the blood of patients with measles, and by Kusama, Yokoyama and Ito from the kidneys of monkeys infected with blood from patients with measles.

From the experiments with the organism I isolated from measles, we find that it is constantly present in measles during the infective period and is not found in other diseases; that specific immune bodies for this coccus are in the blood of patients recovering from measles, and by means of immune rabbit serum these cocci are shown to belong to one biologic group; it produces the same reactions in lower animals as are caused by measles virus; it is isolated from rabbits so infected and the recovered coccus again produces the measles reactions in normal rabbits; animals recovering from the infection produced by this coccus are immune to infection with fresh measles materials; antigens of this organism cause a specific skin reaction in persons with a negative history of measles, and the serum of goats immunized with this coccus [1] appears to protect rabbits and human beings against measles.

COMPRESSION MYELITIS SECONDARY TO ECHINOCOCCUS DISEASE OF VERTEBRAE AND KIDNEY. DR. LAWRENCE E. HINES.

This article will be published in full in a future issue.

DISCUSSION

DR. J. J. MOORE: I wish to emphasize the complement-fixation test for diagnosis. Dr. K. K. Koessler observed a positive skin reaction in a patient whose complement-fixation test was negative.

FURTHER OBSERVATION ON THE RING PRECIPITATION TEST FOR SYPHILIS. DR. RUSSELL D. HERROLD.

The results of further comparative tests with the Wassermann reaction support the view that the ring precipitation test is valuable in detecting syphilis serologically.

Regular Monthly Meeting, Nov. 9, 1925

RUTH TUNNICLIFF, M.D., *President, in the Chair*

SOME OBSERVATIONS ON THE RELATION OF CHEMICAL CONSTITUTION TO BIOLOGIC SPECIFICITY. DRS. JULIAN H. LEWIS and H. GIDEON WELLS.

The cereals — emmer, *Triticum dicoccum;* durum, *Triticum durum;* spelt, *Triticum spelta;* einkorn, *Triticum monococcum* — are genetically related to wheat, *Triticum vulgare.* That einkorn has seven chromosomes, emmer and durum fourteen and wheat and spelt twenty-one, indicates the evolution of these plants by polymerization, and that the fertility or total or partial sterility of interspecies is in accordance with this idea. In like manner, kafir, *Andropogon sorghum,* teosinte, *Euchlaena mexicana,* Schrad and corn, *zea mays,* are botanically related. All these plants yield alcohol-soluble proteins, or prolamines, which have been studied by Gortner and Hoffmann,[2] and which have been found

[1] The bibliography is given in an article entitled "Further Studies on a Diplococcus in Measles," J. Infect. Dis. 37: 193, 1925.

[2] Gortner and Hoffmann: Second Colloid Symposium, Monographs, Chemical Catalogue Co., New York, 1925.

to have marked chemical and physical similarities between those of the wheat group and those of the corn group. Because of these interesting genetic relationships and the chemical and physical similarities and differences between the various members of these two groups, their immunologic relationships are of particular significance and offer an opportunity for further observations on the relation of chemical constitution to biologic specificity. For this purpose the complement-fixation test was used as well as anaphylactic sensitization, determinated by three different methods, i. e., the uterus strip method, the bronchospasm method of Koessler and Lewis, and the usual anaphylactic reaction with guinea-pigs.

For the complement-fixation test, three antiserums were prepared: antigliadin (against the prolamine from wheat), antizein (aganist the prolamine from corn) and antiglutenin (against a non-alcohol-soluble protein from wheat). These antiserums were tested against 1 mg., 0.1 mg., and 0.01 mg. of all the prolamines and glutenin. The results show that the optimal amount of antigen for differentiation is 0.01 mg., and that when this amount is used the prolamines can be separated into a wheat group consisting of gliadin, emmer, durum, spelt and einkorn, and a corn group consisting of zein, teosinte and kafirin. Glutenin appears to be distinct from gliadin, although both are obtained from wheat.

Experiments with the uterus strip method confirmed the results obtained with the complement-fixation test. A uterus from a guinea-pig sensitized with a prolamine from the wheat group reacted with any other prolamine from this group but did not react with the prolamines from the corn group. After a uterus strip had reacted to a protein other than the one with which it had been sensitized, it was completely desensitized to the homologous protein.

The bronchospasm method, which shows graphically the characteristic bronchospasm of anaphylaxis, showed that zein and gliadin do not interact while zein and teosinte do. It also showed that gliadin and glutenin have no antigenic properties in common.

With the anaphylactic reactions it was found that guinea-pigs sensitized with gliadin gave strong reactions when reinjected with the other four proteins of the wheat series, but none with the proteins from the corn series. Animals recovering from these crossed reactions were found to be protected to gliadin just as were the tissues in the uterine strip experiments. Guinea-pigs sensitized with either zein or teosinte and desensitized with a heterologous protein of the same group failed, forty-eight hours later, to react with either the homologous or heterologous protein, indicating that the proteins of this group are similar enough to one another to desensitized animals.

Immunologic study of the alcohol-soluble proteins from certain cereal grains indicate that they fall into two classes. Gliadin from wheat and the prolamines from durum, einkorn, emmer and spelt, of the genus *Triticum*, seem to be closely related, according to tests by means of both the complement-fixation and the anaphylactic reaction (tested by three methods). The alcohol-soluble proteins from common maize, from kafir corn and from teosinte were found to be closely related to one another, but not to the alcohol-soluble proteins of the *Triticum* group. These results agree with the observations made by others (Gortner and Hoffmann) that the chemical properties of these alcohol-soluble proteins indicate the existence of a "wheat group" and a "corn group" of prolamines, the members of each group being chemically similar to each other, as we have found them to be immunologically.

GAUCHER'S DISEASE AND LIPOID HISTIOCYTOSIS. DR. WILLIAM BLOOM.

Dr. Bloom gave a demonstration of specimens and lantern slides from two cases of Gaucher's disease and three cases of lipoid histiocytosis of the Niemann type, stressing the differences between the two conditions. The complete paper will appear in the *American Journal of Pathology*.

DISCUSSION

DR. R. H. JAFFÉ: The histology of Niemann's disease resembles somewhat the lipoid changes found in the internal organs of children dying of malnutrition. The epithelial reticulum cells of the thymus, especially, are enlarged and are filled with lipoid droplets. There are differences as regards the extension of the process and the microchemical reactions of the deposited fat substances, but these may be merely quantitative, the fundamental cause being the same, namely: a severe disturbance of the lipin metabolism. Since the microchemical tests are not reliable, a chemical analysis of the organs in Niemann's disease and malnutrition would be valuable. Chemical studies of the spleen in morbus Gaucher have yielded interesting results.

ANOMALY AND ANEURYSM OF THE CIRCLE OF WILLIS. DR. LAWRENCE JACQUES.

An aneurysm in the circle of Willis accompanied by a marked anomaly of these vessels was reported. The report will appear in a future issue of the ARCHIVES OF PATHOLOGY AND LABORATORY MEDICINE.

DISCUSSION

DR. C. B. SEMERAK: The most frequent anomaly in the circle of Willis is the difference in caliber of the vertebral arteries. This occurs in about 30 per cent of the brains examined. Usually the left vertebral artery is larger, sometimes being as large as the basilar. This anomaly in the width of the vertebral arteries producing an irregular force of circulation may predispose to aneurysm of the basilar artery, and, according to some authors, the aneurysm is generally found in the basilar at the origin of the larger vessel.

THE SPLANCHNOPERIPHERAL LEUKOCYTE BALANCE. DR. W. F. PETERSEN.

The normal level of blood pressure is maintained by an antagonistic orientation of splanchnic and peripheral autonomic impulses. In a similar manner it seems probable that the quantity of leukocytes present at any one time in any particular part of the vascular bed is controlled by a similar antagonism of autonomic impulses. Müller has previously discussed some of the underlying experiments that support this view.

Together with Müller and von Oettingen, we have studied the effect of peripheral stimulation (exposure of abdominal skin of the dog to quartz light) on lymph constituents. It has been found that irradiation is followed by immediate effects apparent in the lymph. These may be predominantly sympathetic in character (increased lymph sugar, lowered lymph protein, diminished calcium) or parasympathetic (decreased lymph sugar, increased protein and calcium). With splanchnic sympathetic orientation there is peripheral leukocytosis; with splanchnic parasympathetic orientation, a peripheral leukopenia. The usual picture is that of a wavelike change with fluctuations between the two extremes. Occasionally the waves are of increasing amplitude.

In a second group of animals, eye pressure was made with thoracic incanulation. In all instances the heart rate was slowed to approximately 50 per cent of the normal rate, parasympathetic simuation. The lymph effect that followed might be either sympathetic or parasympathetic. Usually there were marked fluctuations between the extremes. The peripheral leukocyte count again indicated an antagonistic state from that obtaining in the splanchnic area. The possible mechanism by which the rapid fluctuation of the leukocytic curve takes place was discussed.

DISCUSSION

DR. E. R. LECOUNT: Are these variations of the sugar and calcium associated with a constancy in the osmotic pressure of the lymph? This inquiry is made because I understand that the osmotic pressure of the blood is maintained at a rather constant level, but I do not know that a similar condition obtains with the lymph.

DR. PETERSEN: No osmotic pressure measurements have been made, but in certain experiments the electrical conductivity has not changed, and probably there are no changes in osmotic pressure.

Book Reviews

Die Individualität des Blutes in der Biologie, in der Klinik und in der gerichtlichen Medizin. Von Dr. Leone Lattes, Professor an der Universität Modena. Paper. Price, 9.60 marks. Pp. 226, with 48 illustrations. Berlin: Julius Springer, 1925.

This is a revision and enlargement of Lattes' monograph in Italian which appeared in 1923. After a brief introductory discussion of constitutional and acquired conditions of the blood which characterize the individual, the author proceeds to a consideration of iso-agglutination, the phenomenon on which the human blood groups depend, as the important constitutional characteristic of the blood.

This important reaction is taken up under five main headings, the first of which relates to the theoretical and biologic factors concerned in iso-agglutination; to the fixity of the blood groups, and to quantitative and qualitative differences in iso-agglutination which may explain some of the recently described variants or subdivisions of the original and usually accepted four groups; and to the relationship of iso-agglutination to pseudo-agglutination and auto-agglutination and to isohemolysis, complement fixation, and hetero-agglutination and hetero-hemolysis. Lattes concludes that none of the data thus far published which tend to indicate the existence of more than four blood groups or of subdivisions of these groups, will withstand critical analysis.

The second main division discusses the inheritability of the blood group characteristics, the conception of von Dungern and Hirschfeld that the blood group of the individual is the result of the combination of two pairs of allelomorphs, being accepted and elaborated. Since the presence of one or the other of the two agglutinogens is dominant over its absence, the nine genotypes possible according to the mendelian law become reduced to four phenotypes, which are the four blood groups as we know them. Striking evidence of the author's painstaking use of the literature of his subject is his tabulation and critical analysis of previously published studies of the blood groupings of 1,808 children resulting from 862 parental pairs whose groups had also been determined. An interesting minor fact is that this total of recorded parental pairs includes only one group 4 pair. In this large material, only twenty-nine children deviated from the mendelian formula. It is significant that all of these exceptions were reported by seven of the total number of investigators whose results are analyzed, and that the total number of cases studied by them constitute only a small fraction of all the cases investigated. Although Lattes believes that illegitimacy, faulty technic or weak agglutinative properties may explain all or some of these discrepancies, he concludes that until the possibility of the occurrence of exceptions is disproved, in medicolegal usage the blood group cannot be quite absolute evidence of the parentage of a child. In an appendix he discusses in detail, as a possible explanation of the discrepancies, Bernstein's recent conception that the blood groups are the result of the combination of three allelomorphs, of which one is recessive.

The next division of the monograph is devoted to iso-agglutination as an ethno-anthropologic characteristic. Among Europeans, including Americans of European origin, group 1, characterized by nonagglutinability of the cor-

puscles, constitutes from 35 to 45 per cent. of the total; among Asiatics, from 25 to 35 per cent. In certain pure primitive races, namely, aboriginal Australians, Philippine Malays and American Indians, this group predominates strongly, forming from 57 to 78 per cent. of the total. Group 2 predominates over group 3 in the European races, whereas the relationship is reversed among Asiatics. The biochemical racial index of the Hirszfelds, which is the quotient obtained by dividing the sum of group 2 and group 4 in a given population by the sum of group 3 and group 4, varies from 2.5 to 3 for Europeans and Americans to 1 and less than 1 for Asiatics and Africans. The ethnographic variation in the distribution of the blood groups is held to be the result of varying degrees of intermingling of two primitive races, a Western and an Eastern, characterized by the presence, respectively, of agglutinogen A (group 2) and agglutinogen B (group 3).

The section devoted to the clinical bearing of iso-agglutination discusses the causes of the untoward results of blood transfusion, and the technic of blood transfusion and of compatibility determination. The pioneer work of Americans in this field receives full recognition.

The final subdivision relates to the medicolegal applications of iso-agglutination. The phenomenon may be used to establish the parentage, more particularly the paternity, of a child, or the origin of a blood stain. It is with the latter subject that many of Lattes' own investigations have dealt. In blood stain diagnosis the human origin of the blood must first be established. Since the iso-agglutinins are fairly resistant, an extract of a blood stain may exhibit the agglutinative properties of the original blood for a considerable period. Such extracts, however, have a strong tendency to cause pseudo-agglutination, a disturbing factor which can be overcome, according to Lattes' own investigations, by the addition of lecithin emulsion to the suspended corpuscles which are to be tested. Granted that the stain has not lost its agglutinative properties, it is possible to determine whether a given stain may be or definitely is not the same as the blood of a given individual. If the stain was made by a group 4 blood, difficulties may arise because such blood normally is devoid of agglutinins. Establishing the group 4 nature of a given stain, and thus proving that the failure of an extract of such a stain to agglutinate human corpuscles is not due to a loss of pre-existing agglutinative properties, is possible by permitting the agglutinogens of the corpuscular remnants of the stain to absorb the agglutinins of known group 2 and group 3 serums. The technic of the application of iso-agglutination to blood stain diagnosis is described in detail by the author.

In an eleven page appendix, Schiff describes the status of blood group determination in German medicolegal practice. The forensic application of blood grouping may be nullified by the fact that in both civil and criminal actions the consent of the individual whose blood is to be tested is necessary for withdrawal of blood for this purpose. The same provision would probably apply in American legal usage. For the purpose of determining the possible origin of a blood stain, by comparison with the blood of a given individual, the iso-agglutination phenomenon may be used to prove that the stain and a given blood sample may come from the same person or must come from different persons. In questions relating to the parentage of a child the procedure has relatively little value in determining the mother, unless the paternity of the child is beyond all doubt. In the establishment of the paternity of a child, in civil or criminal actions involving illegitimacy and matters relating thereto, the iso-agglutination reaction has greater applicability and value. The blood groups of mother and

child being known, the reaction may be used to determine whether a given man *may* be the father of the child, which would have only corroborative value, or whether he *cannot* be the father, evidence of definitely conclusive value.

To the 190 pages of text is appended a thirty page bibliography containing 700 titles. That this is not a mere compilation is evident from the text; it is apparent in many instances that the author has subjected published material to more thorough and critical analysis than it received at the hands of the original writers. Especially to be commended is the clarity and directness of the German in which the monograph is written. The involved circumlocutions which Carlyle satirized so well in "Sartor Resartus" are entirely absent, probably because Italian, rather than German, appears to be the author's native language.

PATHOLOGY OF THE MOUTH. By FREDERICK B. MOOREHEAD, D.D.S., M.D., Professor of Oral Surgery and Pathology, and KAETHE W. DEWEY, M.D., Assistant Professor of Pathology, College of Dentistry, University of Illinois, Chicago. Cloth. Price, $7.00 net. Octavo. Pp. 540, with 213 illustrations. Philadelphia: W. B. Saunders Company, 1925.

In their preface the authors declare that "speaking technically, the mouth is neglected territory." The dental student, so much of whose time is devoted to technical dentistry, has had scant training in pathology and none in general medicine. The medical student, on the other hand, giving most of his attention to pathologic processes in more vital organs, has had little instruction in diseases of the mouth. Whether the reader is convinced that "next to the eye, the mouth is the most complex structure in the body and should have as large a place in the medical curriculum as ophthalmology, otology, orthopedic surgery, etc.," the authors are deserving of high praise for their effort to present for the first time in English and in a single volume the pathology of "the mouth, both in its local and interdependent relations, its primary and secondary lesions," without reference to treatment.

The book is divided into two parts. Part I comprises the first 288 pages and is concerned with general diseases, and Part II with tumors of the mouth. The book is remarkably free from typographical errors. The large type and unusually wide spacing between lines has increased the size of the volume but has added much to the ease of reading.

The volume is copiously illustrated. Nine of the 213 illustrations are in colors. Most of these illustrations are well chosen. In figure 43, the cells are not all drawn to the same scale, and this may be confusing to students. The same cells, shown in figure 107, are in their proper proportions. Figure 151 is presented as an illustration of a lymphosarcoma of the tongue. It certainly has more resemblance to an acute inflammation, and was so diagnosed by four experienced pathologists to whom it was submitted. Figure 155 would be (and has been) diagnosed as an endothelioma by many pathologists. It is to be hoped that in future editions of the book these illustrations will be replaced by others more typical of the lesion. It is a matter of surprise and regret that the use of material for certain illustrations is credited to the curator of a museum rather than to the museum itself or to the physician or dentist originally responsible for the specimen.

The various subjects presented in Part I are, on the whole, satisfactorily discussed. One of the least satisfactory chapters is that entitled, "Inflammations and Granulation Tissue," to which about ten pages are devoted. This is neither a simple statement of the elementary principles of inflammation and granula-

tion tissue, nor a more advanced presentation of the more difficult and still debated problems concerning these conditions, although it attempts to be both. The chapter on "Periodontitis and Alveolar Abscess" is both well illustrated and well written; that on "Pyorrhea alveolaris" is copiously and excellently illustrated, but somehow did not leave a clear-cut conception of the lesion in the mind of the reviewer. The portion of Part I which will be most interesting and helpful to physicians is those chapters dealing with pathologic conditions in the mouth associated with acute and chronic diseases in other parts of the body. Some of the statements concerning the glands of internal secretion are more dogmatic than our present knowledge would seem to justify.

In Part II, 218 pages are devoted to the presentation of tumors that occur in the mouth. The chapter on "Benign Giant-Cell Tumor or Giant-Cell Sarcoma" deserves special mention. In the chapter on "Odontomas," one regrets that no reference is made to the truly remarkable collection of these growths by Dr. T. L. Gilmer.

Fifteen pages of bibliography are appended. This is the least well edited portion of the book. Gilmer's article on odontomas is not mentioned in the portion of the bibliography devoted to that subject, but is found with the subject of gingivitis. A reference to "Borst, Pathologische Anatomie, 1913, I, 720," is in reality to Borst's article on "Echte Geschwülste" in Aschoff's "Pathologische Anatomie." These are examples of discrepancies in the bibliography.

In spite of the criticisms, the book as a whole represents a creditable effort to present the subject of the pathology of the mouth.

BIOCHEMISCHE GRUNDLAGEN DER DISPOSITION ZUM KARZINOM. By ERNST FREUND and GISA KAMINER. Pp. 85. Vienna: Julius Springer, 1925.

On eighty-five pages the authors summarize the results of fifteen years of their research. It began with the discovery of the lytic action of normal human serum on cancer cells. Unlike the discoveries of other diagnostic methods, the nature of the reaction seemed to interest the authors from the very beginning more than its immediate practical application. The last stage of their work resulted in the artificial production of the lytic substance — a saturated dicarbonic acid (perhaps dekamethylendicarbonic) — and of another nonsaturated fatty acid, which protects the cancer cells against the action of normal serum. Both substances originate in the intestine, and palmitin seems to be their chief source. Interesting parallels and differences between sarcoma and carcinoma have been developed. To describe their discoveries fully would require perhaps half the space their booklet contains. This praise is at the same time the only objection that can be raised against it, which is unusual in this age of mass production. With about 400 pages, the book could contain sufficient technical details to induce a flood of control research which might prove that Freund and Kaminer's discoveries are just interesting accidental facts. There is, however, a possibility that they are of fundamental importance.